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## 2 **The Dutch Working Party on Antibiotic Policy (SWAB) guidelines for** 3 **empirical antibacterial therapy of sepsis in adults – 2026 update**

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46 NVMM: Nederlandse Vereniging voor Medische Microbiologie (Dutch Society of Medical  
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51 Spoedeisende Hulp Artsen (Dutch Society of Emergency Physicians)

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54 Sections that are changed compared to the 2020 SWAB Sepsis guidelines are highlighted in yellow.

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## 116 Summary and what's new in comparison with the previous sepsis 117 guideline

118  
119 The Dutch Working Party on Antibiotic Policy (SWAB) in collaboration with the Dutch Society of Medical  
120 Microbiology, the Netherlands Society of Internal Medicine, the Dutch Society for Intensive Care, the  
121 Dutch Society for Surgery, the Dutch Society of Hospital Pharmacists and the Dutch Society of  
122 Emergency Physicians, has updated the Dutch evidence-based guidelines on antibacterial therapy of  
123 sepsis in adults.

124 These guidelines are written for adult patients with *bacterial* sepsis according to the Sepsis-3 criteria.<sup>1</sup>  
125 Some causes of sepsis are not included, such as neutropenic sepsis, osteomyelitis, meningitis,  
126 mediastinitis and endocarditis. We also did not provide recommendations on patients with sepsis and  
127 intravascular prosthetic material or long-term central venous catheters.

128 The guideline is based on 10 population, intervention, comparison, and outcomes (PICO) questions  
129 relevant for the Dutch clinical setting that the committee generated (**Table 1**). For each question we  
130 performed evidence summaries, which were assessed using the Grading of Recommendations  
131 Assessment, Development, and Evaluation (GRADE) system. Quality of evidence for clinically relevant  
132 outcomes was graded from high to very low. The committee formulated recommendations after  
133 structured discussions as strong or weak. When evidence could not be obtained, recommendations  
134 were provided on the basis of opinions and experiences (good practice statements).

135 The 2026 SWAB sepsis guidelines were partially revised in comparison to the 2020 version. For the  
136 revision of the guideline in 2026, we updated 5 chapters: chapters 1, 2 and 3 on causative bacterial  
137 pathogens of sepsis in the Netherlands and their antibacterial resistance patterns; chapter 8 on the  
138 optimal duration of antibiotic treatment, with a focus on patients with gram-negative bacteraemia;  
139 and chapter 9 on pharmacokinetic / pharmacodynamic dosing considerations, with a focus on whether  
140 prolonged use of beta-lactam antibiotics is superior to intermittent administration. In addition, we  
141 removed chapter 7 on the approach to patients with sepsis and a suspected penicillin allergy, as the  
142 SWAB guideline for the approach to suspected Antibiotic Allergy was developed in 2022, to which we  
143 now refer in chapter 6.<sup>2</sup> Based on this process, the guideline includes 56 recommendations on the  
144 antibacterial management of sepsis in adults (see recommendations below).

145 The committee would like to underscore the difficulty of providing evidence-based recommendations  
146 regarding ESBL coverage for patients with sepsis. In the Netherlands, the probability of the causative  
147 pathogen producing ESBL enzymes is an important variable in the choice of empirical treatment. 3GCR-  
148 E is often used as a proxy for ESBL-production. National surveillance data from 2024 showed that 9%  
149 of *Escherichia coli* and 14% of *Klebsiella pneumoniae* blood isolates were resistant to 3<sup>rd</sup> generation  
150 cephalosporins. However, Dutch research has shown that it is difficult to predict whether the causative  
151 pathogen will be a 3GCR-E in a patient with sepsis and that in community-acquired sepsis, excluding  
152 patients with prior 3GCR-E colonisation or infection, the risk of 3GCR-E involvement is very low. The  
153 committee recommends to cover 3GCR-E in patients if prior (1-year) culture revealed 3GCR-E. In  
154 patients without prior (1-year) cultures showing 3GCR-E the decision to empirically cover 3GCR-E  
155 should be made on an individual patient basis taking into account multiple risk factors. Due to the  
156 steep increase in ceftriaxone resistance in *Klebsiella pneumoniae* in blood cultures in 2024, we added

157 a new recommendation in the update of the guidelines to consider antibacterial therapy escalation in  
158 patients with persistent sepsis when *K. pneumoniae* is cultured, pending susceptibility results.

159 In current clinical practice the choice of empirical antibacterial treatment of sepsis differs considerably  
160 between hospitals, varying from a third generation cephalosporin, piperacillin-tazobactam, a  
161 combination of a second/third generation cephalosporin with short-term treatment with an  
162 aminoglycoside, a combination of a second or third generation cephalosporin with a fluoroquinolone  
163 to a carbapenem. The final choice is therefore dictated by the likelihood of involvement of a resistant  
164 causative pathogen, by the desire to avoid the use of third-generation cephalosporins,  
165 fluoroquinolones and/or carbapenems from an antibiotic stewardship perspective and by risks of  
166 toxicity and other potential adverse events for the patient.

167 We therefore cannot provide strong recommendations on the best empirical treatment in sepsis based  
168 on the currently available literature. We found only subtle differences between strategies on clinical  
169 outcomes in studies that were also frequently not generalizable to the Dutch clinical setting. Every  
170 strategy has advantages and disadvantages depending on the mentioned perspectives (resistance  
171 epidemiology, pharmacokinetic/pharmacodynamic (PK/PD) properties, antibiotic stewardship,  
172 adverse events). Consequently, the committee provided pragmatic suggestions for empirical  
173 treatment choices in patients with sepsis based on current evidence, reported resistance rates  
174 nationally, the antibiotic stewardship perspective and risk of adverse events.

175 In patients with sepsis, we generally recommend using a beta-lactam antibiotic covering the most likely  
176 involved pathogens. Also, we recommend to cover pathogens in prior (1-year) relevant cultures in  
177 general. We added suggestions on empirical therapy for *Pseudomonas aeruginosa*, *Staphylococcus*  
178 *aureus* and *Enterococcus* spp.

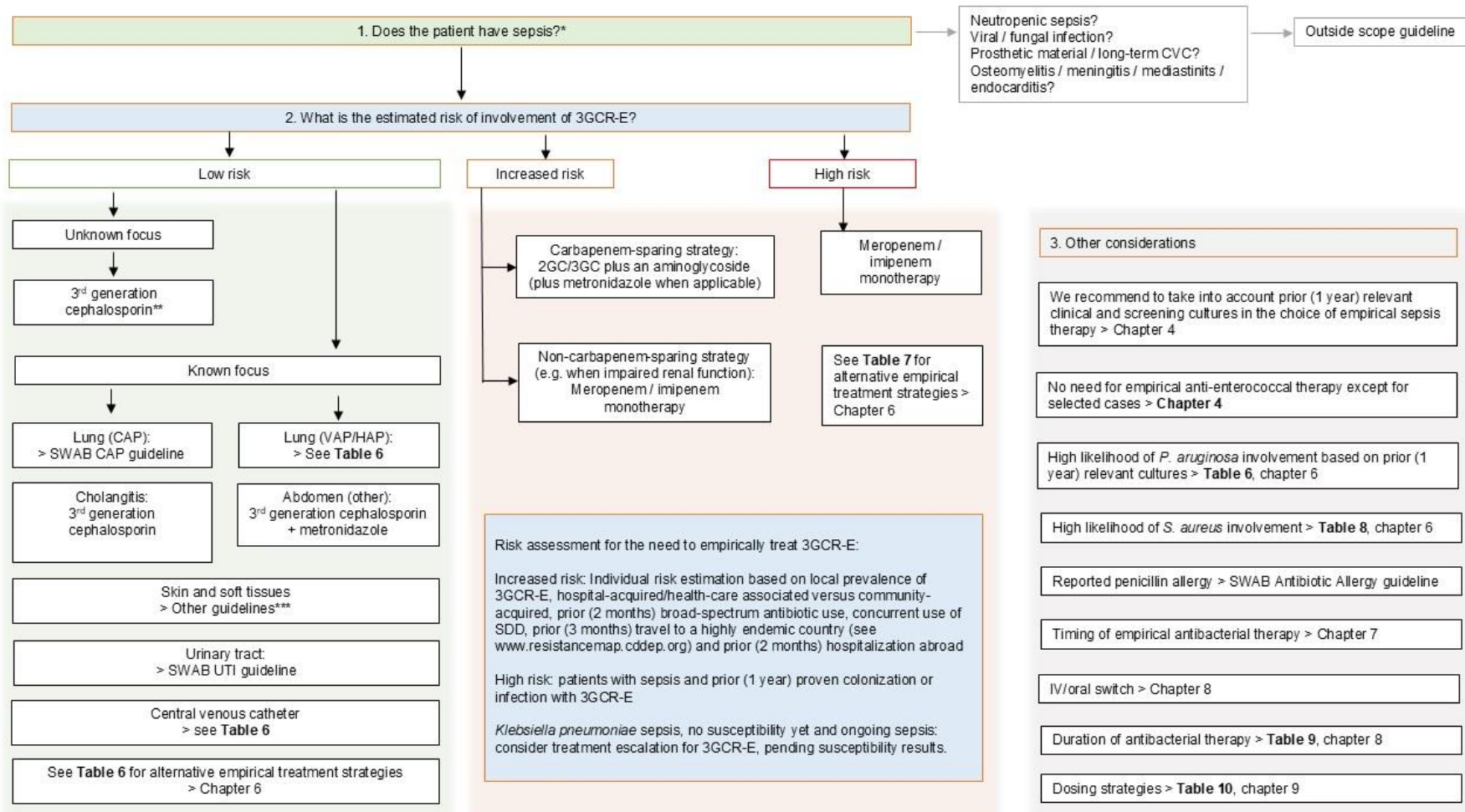
179 Similarly, we provided pragmatic suggestions for the optimal timing to start empirical antibacterial  
180 treatment in a patient with sepsis. Based on new studies, we were able to generally recommend on  
181 shorter treatment durations of patients with sepsis in comparison with the previous guidelines. The  
182 committee also underscores the responsibility of clinicians to de-escalate antibacterial therapy in  
183 patients with sepsis, especially when very broad spectrum has been started. Due to toxicity concerns,  
184 we strongly recommend to stop empirical aminoglycoside treatment after two days.

185 The previous SWAB sepsis guideline suggested an antibacterial treatment duration of 7 days for most  
186 patients with gram-negative bacteremia. Recently supported by high-quality evidence, this has now  
187 lead to a strong recommendation in the updated guidelines regarding the treatment duration for  
188 patients with Enterobacterales bacteraemia, including sepsis.

189 Among recommendations on PK/PD considerations in patients with sepsis, we continue to recommend  
190 prolonged use of beta-lactam antibiotics over intermittent dosing in critically ill patients with sepsis.  
191 This recommendation is now supported by a stronger body of evidence compared with the evidence  
192 available at the time of the previous guideline. Therapeutic drug monitoring is recommended for all  
193 patients on aminoglycoside and vancomycin treatment.

194 A flow chart is provided in **Figure 1** which summarizes the given recommendations on the empirical  
195 antibacterial treatment of sepsis.

196 **Figure 1. Flow chart of guideline recommendations on empirical antibiotic treatment of sepsis**



213 \* For the diagnosis and non-antibiotic treatment of sepsis we refer to the Dutch guideline 'Sepsis fase 1'.<sup>3</sup> \*\* For this guideline 3GC includes ceftriaxone and cefotaxim and  
214 does not include the anti-pseudomonal cephalosporin ceftazidime. \*\*\* Guidelines on skin and soft tissue infections.<sup>4,5</sup> Abbreviations: 3GCR-E: 3rd generation cephalosporin-  
215 resistant Enterobacterales; 2GC: second generation cephalosporin; 3GC: 3rd generation cephalosporin; SDD: selective decontamination of the digestive tract.

216 **Recommendations**

217

218 **I Causative bacterial pathogens in sepsis**

219 Which patients are at risk for sepsis due to third-generation cephalosporin-resistant Enterobacterales

220 or *P. aeruginosa* in the Netherlands? (chapter 3)

Recommendation	Strength	Quality of evidence
1. We recommend empirical therapy against 3GCR-E in patients with sepsis and prior (1 year) proven infection or colonization with 3GCR-E	Strong	Very low
2. We suggest that clinicians take into account the risk of 3GCR-E involvement in sepsis on an individual patient basis to decide if empirical antibacterial therapy against 3GCR-E is appropriate  Factors to guide this decision include local prevalence of 3GCR-E, if the infection is hospital-acquired/health-care associated versus community-acquired, prior (2 months) broad-spectrum antibiotic use, concurrent use of SDD, prior (3 months) travel to a highly endemic country (see <a href="https://resistancemap.cddep.org/">https://resistancemap.cddep.org/</a> ) and prior (2 months) hospitalization abroad	Weak	Very low
3. We suggest to consider escalation of antimicrobial therapy in patients with persistent sepsis on 3rd generation cephalosporin treatment when a relevant <i>K. pneumoniae</i> isolate has been cultured, pending susceptibility results	Weak	Very low
4. We recommend empirical therapy against <i>P. aeruginosa</i> in patients with sepsis and prior (1 year) infection or colonization with <i>P. aeruginosa</i>	Strong	Very low

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222 **II Empirical antibacterial therapy in sepsis**

223 What is the importance of appropriate empirical therapy in patients with sepsis? (chapter 4)

Recommendation	Strength	Quality of evidence
5. We recommend empirical broad-spectrum antibacterial therapy for patients presenting with sepsis to cover all pathogenic bacteria that are likely to be involved	Strong	Moderate
6. We recommend to take into account prior (1 year) resistance in relevant clinical and screenings cultures in the choice of empirical sepsis therapy	Strong	Very low
7. We recommend that empirical antibacterial therapy is guided by the local distribution of pathogens associated with sepsis and their antimicrobial susceptibilities	Strong	Very low

8. We suggest empirical antibacterial therapy for patients presenting with sepsis to cover HRMO when these are likely to be involved	Weak	Very low
9. We suggest empirical antibacterial therapy covering anaerobic bacteria for patients presenting with sepsis and intra-abdominal infections of the lower intestinal tract or necrotizing soft tissue infections	Weak	Very low
10. We generally suggest against routine empirical treatment of anaerobic bacteria in patients presenting with sepsis due to aspiration pneumonia, unless empyema or a lung abscess is suspected	Weak	Very low
11. We generally recommend against routine empirical treatment of enterococci in patients presenting with sepsis	Strong	Moderate
12. We suggest that anti-enterococcal therapy could be considered in individual patients with sepsis, e.g. those who have a high likelihood of enterococcal involvement based on recent relevant cultures and those with recent complicated intra-abdominal surgery or a suspected CVC infection and substantial exposure to broad spectrum antibiotics	Weak	Very low

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225 What is the effect of double active empirical antibacterial therapy compared to monotherapy in

226 patients with sepsis? (chapter 5)

<b>Recommendation</b>	<b>Strength</b>	<b>Quality of evidence</b>
13. We recommend against routine double active empirical antibacterial therapy* for patients with sepsis or septic shock.	Strong	Moderate
14. We suggest that double active therapy is not routinely used as definite therapy for patients with sepsis due to <i>P. aeruginosa</i> infection	Weak	Very low
15. We suggest that double active therapy is not routinely used as definite therapy for patients with sepsis due to <i>S. aureus</i> infection not associated to prosthetic material	Weak	Moderate

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234 What is the optimal choice of empirical therapy in patients with sepsis in the Netherlands? (chapter 6)

235 Antibacterial therapy in patients with sepsis in general

<b>Recommendation</b>	<b>Strength</b>	<b>Quality of evidence</b>
16. In patients with sepsis, we generally recommend using a beta-lactam antibiotic covering the most likely involved pathogens	Strong	Moderate

17. In patients with sepsis in general / with no obvious source of infection, we suggest a 3rd generation cephalosporin (3GC). Alternative empirical treatment strategies are listed in <b>Table 6</b>	Weak	Low
18. In patients with sepsis due to HAP or VAP, we suggest that there are equivalent empirical treatment strategies, listed in <b>Table 6</b>	Weak	Low
19. In patients with sepsis due to cholangitis, we suggest a 3GC. Alternative empirical treatment strategies are listed in <b>Table 6</b>	Weak	Low
20. In patients with sepsis due to intra-abdominal infection, we suggest a combination of a 3GC with metronidazole. Alternative empirical treatment strategies are listed in <b>Table 6</b>	Weak	Low
21. In patients with sepsis and a suspected CVC infection*, we recommend prompt removal of the line	Strong	GPS
22. In patients with sepsis and suspected CVC infection, we suggest empirical treatment with a 3GC** with gentamicin or high dose ciprofloxacin Alternative treatment strategies are listed in <b>Table 6</b>	Weak	GPS
23. For the empirical treatment of sepsis due to UTI, CAP and SSSI's and for patients with sepsis and suspected antibiotic allergy, we refer to other guidelines <sup>2, 4-7</sup>		

236 \* Recommendations for sepsis due to suspected long-term CVC's were not included in this guideline

237 \*\* 3GC may be given in high dose for more optimal PK/PD for *S. aureus* infections in accordance to EUCAST

238 *Antibacterial therapy in patients with sepsis and increased risk of involvement of 3GCR-E*

24. In patients with sepsis and high risk of involvement of 3GCR-E based on prior (1 year) infection/colonization, we recommend meropenem or imipenem as empirical antibacterial therapy. Alternative strategies are listed in <b>Table 7</b>	Strong	Moderate
25. In patients with sepsis and increased risk of involvement of 3GCR-E but no prior (1 year) infection/colonization, we suggest that a carbapenem-sparing strategy (listed in <b>Table 7</b> ) is acceptable	Weak	Very low
26. We cannot provide a recommendation for or against empirical or definite treatment with piperacillin-tazobactam in patients with sepsis due to chromosomal AmpC-producing Enterobacterales (such as <i>Enterobacter</i> , <i>Serratia</i> , <i>Citrobacter</i> , <i>Providencia</i> and <i>Morganella</i> spp)	-	-
27. In patients with sepsis due to ESBL-producing Enterobacterales, we recommend against piperacillin-tazobactam as definite antibacterial therapy regardless of the in vitro susceptibility	Strong	Moderate

239

240 *Antibacterial therapy in patients with sepsis and increased risk of involvement of Staphylococcus aureus*

28. There is insufficient evidence to recommend against empirical use of other beta-lactam antibiotics than flucloxacillin or ceftazolin in patients with sepsis in which <i>S. aureus</i> is a likely pathogen. Empirical sepsis treatment strategies when there is a substantial risk of <i>S. aureus</i> involvement are listed in <b>Table 8</b>	-	-
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29. For definite therapy of patients with sepsis due to <i>S. aureus</i> , we refer to the Dutch guideline on <i>S. aureus</i> bacteraemia. <sup>8</sup>		
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243 **III Timing and duration of antibacterial therapy in sepsis**

244 What is the optimal timing of empirical antibacterial therapy in patients with sepsis? (chapter 7)

<b>Recommendation</b>	<b>Strength</b>	<b>Quality of evidence</b>
30. In patients with sepsis or septic shock, we recommend that the administration of antibacterial treatment should be initiated promptly with health care systems working to reduce that time to as short a duration as feasible	Strong	Low

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246 What is the optimal duration of antibacterial treatment for sepsis? (chapter 8)

<b>Recommendation</b>	<b>Strength</b>	<b>Quality of evidence</b>
31. For treatment duration of sepsis due to CAP, UTI, SSSI and of sepsis due to <i>S. aureus</i> infection, we refer to other guidelines <sup>4-9</sup>		
32. We recommend source control interventions when possible to support antibacterial treatment in patients with sepsis.	Strong	Low
33. We recommend that a four-day course of antibacterial treatment is appropriate for patients with sepsis due to intra-abdominal infections following effective source control and with favourable clinical response	Strong	Moderate
34. We suggest that shorter courses of antibacterial treatment (up to three days) are appropriate in patients with sepsis and cholangitis following adequate drainage of the biliary tree	Weak	Very low
35. We recommend that an antibacterial treatment duration of 7 days is adequate for most patients with sepsis due to VAP	Strong	Moderate
36. We suggest that an antibacterial treatment duration of 7 days is adequate for most patients with sepsis due to HAP	Weak	Very low
37. We suggest that an antibacterial treatment duration of 7 days at maximum is adequate for most patients with sepsis due to suspected CVC infection with gram-negative pathogens following removal of the CVC and with favourable clinical response	Weak	Very low
38. We suggest that an antibacterial treatment duration of 0 to 7 days is adequate for most patients with sepsis due to suspected CVC infection with CNS or enterococci following removal of the CVC and with favourable clinical response	Weak	GPS
39. We recommend that an antibacterial treatment duration of 7 days is adequate for most patients with Enterobacterales bacteraemia, including sepsis, unless the underlying diagnosis or lack of source control requires a longer or shorter duration	Strong	Moderate-high

40. We suggest that an antibacterial treatment duration of 7 days is adequate for sepsis and septic shock without a clear focus in most patients with favourable clinical response	Weak	Low
41. We recommend daily assessment for the need of antibacterial therapy in patients with sepsis and to discontinue therapy when during follow-up there is lack of clinical or microbiological evidence of infection	Strong	GPS
42. We suggest that procalcitonin levels are used to support shortening the duration of antibacterial therapy in patients with sepsis if optimal duration of antibiotic therapy is unclear	Weak	Moderate
43. We recommend to consider antibiotic de-escalation (resulting in smaller spectrum antibiotics) in all patients on antibiotics for sepsis on a daily basis and based on pathogen identification, sensitivities and risk of adverse events	Strong	Very low
44. We recommend to stop empirical aminoglycoside therapy within a maximum of two days	Strong	Low
45. We recommend to switch systemic antibiotic therapy from intravenous to oral antibiotic therapy after 48 -72 hours on the basis of the clinical condition and when oral treatment is feasible	Strong	Very low

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#### 248 **IV Pharmacokinetic and pharmacodynamic considerations in sepsis**

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250 In patients with sepsis, should we recommend pharmacokinetic/pharmacodynamic dosing  
 251 optimization for empirical antibacterial therapy? (chapter 9)

<b>Recommendation</b>	<b>Strength</b>	<b>Quality of evidence</b>
46. In patients with sepsis, we suggest that dosing strategies of antibacterial therapy be optimized based on accepted pharmacokinetic / pharmacodynamic principles and specific drug properties ( <b>Table 10</b> )	Weak	Low
47. For adults with sepsis or septic shock treated on the intensive care unit, we recommend prolonged infusion of piperacillin-tazobactam or carbapenems for maintenance (after an initial loading dose) rather than bolus administration.	Strong	High
48. For adults with sepsis or septic shock treated on the intensive care unit, we suggest prolonged infusion rather than bolus administration for other beta-lactams such as cephalosporines/penicillins, taking their pharmacokinetic properties into account.	Weak	Low to moderate
49. In patients with sepsis, we recommend direct therapeutic drug monitoring (including either mid-dosing or both peak and trough levels) during aminoglycoside treatment in patients with sepsis and septic shock	Strong	GPS

50. In patients with sepsis, we recommend therapeutic drug monitoring during vancomycin treatment in patients with sepsis and septic shock	Strong	GPS
51. In patients with sepsis, we suggest therapeutic drug monitoring when there are concerns on target attainment of other antibacterial drugs than aminoglycoside and vancomycin (e.g. extreme body weight, augmented or decreased renal clearance, hypoalbuminemia)	Weak	GPS
52. In patients with sepsis, we suggest continuous* infusion of vancomycin	Weak	GPS
53. In patients with sepsis in whom ciprofloxacin is indicated, we suggest empirical ciprofloxacin three times daily 400 mg iv	Weak	GPS

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\* Continuous infusion includes one intermittent dose as a loading dose

CONCEPT

## 254 **Introduction and methodology**

### 255 **General introduction**

256 Sepsis is currently defined as life-threatening organ dysfunction caused by a dysregulated host  
257 response to infection.<sup>1, 10, 11</sup> Sepsis and septic shock are common reasons for intensive care unit (ICU)  
258 admission and have high mortality rates, even at long-term follow-up.<sup>12-19</sup> In 2004, the estimated  
259 annual number of admissions for severe sepsis in Dutch ICU's was 7700 to 9500.<sup>20</sup> The incidence of  
260 sepsis may have risen in recent decennia, possibly due to ageing and increasing numbers of  
261 immunocompromised patients.<sup>13, 15, 21</sup> Antibacterial therapy is an essential part of effective sepsis  
262 treatment. Inappropriate or delayed antibacterial treatment in patients with sepsis and septic shock  
263 are associated with increased morbidity and mortality.<sup>22-27</sup>

264  
265 The Dutch Working Party on Antibiotic Policy (SWAB), initiated by the Dutch Association of Internal  
266 Medicine, the Dutch Society for Medical Microbiology and the Dutch Association of Hospital  
267 Pharmacists, coordinates activities in the Netherlands with the aim to optimize antibiotic use, to  
268 contain the development of antimicrobial resistance, and to limit the costs of antibiotic use. For this  
269 purpose, SWAB develops evidence-based guidelines on antibiotic treatment, intended for the Dutch  
270 situation. SWAB also yearly reports on the use of antibiotics and on trends in antimicrobial resistance  
271 in The Netherlands in NethMap (available from [www.swab.nl](http://www.swab.nl)), in collaboration with the Centre for  
272 Infectious Diseases Control, National Institute for Public Health and the Environment (CIb-RIVM).<sup>28</sup>

273  
274 The general objective of the SWAB sepsis guideline is to guide medical professionals in empirical  
275 antibacterial treatment for adults with sepsis and septic shock in hospitals in the Netherlands. **The**  
276 **current guidelines on empirical antibacterial therapy of sepsis in the Netherlands is an update of the**  
277 **SWAB sepsis guidelines published in 2020.**<sup>29</sup> The first step for the update included the establishment  
278 of a guideline committee with individuals from all relevant Dutch professional medical societies  
279 involved in the care for adults with sepsis. The group included experts in the field of sepsis and  
280 methodology.

### 281 282 **Scope and target audience**

283 The guideline articulates the prevailing professional standard in sepsis and contains general  
284 recommendations for the antibacterial treatment of hospitalized adults. Sepsis is a complex syndrome  
285 that can originate from multiple sites of infection. Patients with sepsis comprise a very heterogeneous  
286 population and in the individual patient there are always nuances and uncertainties in the ultimate  
287 diagnosis of sepsis. It is therefore possible that these recommendations are not applicable in an  
288 individual patient case. The applicability of the guideline in clinical practice is the responsibility of the  
289 treating physician. There may be facts or circumstances when non-adherence to the guideline is  
290 desirable in the interest of good patient care.

291  
292 We aimed to provide an overview of the quality of available evidence and give evidence-based  
293 recommendations for empirical treatment of sepsis in adults ( $\geq 18$  years old). We restricted the  
294 guideline to the most important causes of sepsis. Pneumonia is the most common source of sepsis in  
295 adults, followed by abdominal infections, urinary tract infections (UTI) and complicated skin and soft  
296 tissue infections (SSTI).<sup>14, 16, 30-32</sup> In addition, we included sepsis in general or of (yet) unknown origin  
297 and a separate chapter on sepsis and suspected central venous catheter infection. The definitions used  
298 in this guideline are specified in the next section.

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The SWAB sepsis guideline cannot be applied to children with sepsis nor to patients with sepsis due to viral or fungal infections. For these infections we refer to the SWAB guideline on fungal infections<sup>33</sup> and guidelines on treating specific viral infections, like Influenza.<sup>34</sup> Other populations that are excluded from the guideline are patients with neutropenic fever or sepsis and patients with sepsis due to central venous catheters for long term venous access (e.g. port-a-cath, Broviac). This guideline doesn't include recommendations on the *diagnosis* of sepsis; treatment of sepsis other than antibacterial treatment, including interventions on source control; monitoring of sepsis; and care after recovery of sepsis. For recommendations on these topics, we refer to the general Dutch sepsis guideline of which this SWAB guideline is a component, initiated by the NIV, and of which the concept of the first phase was recently distributed.<sup>3</sup>

The guideline committee defined the scope of the guideline and key questions to be answered. The definite list of key questions was based on key questions in the previous version of the guideline and priorities for clinical practice. **Table 1** shows the final key questions. Questions covering interventions were structured into the PICO format (Population; Intervention; Control; Outcomes, see appendix). Guideline committee members were assigned to one or more key questions.

**Table 1. Key questions SWAB guideline for empirical antibacterial therapy of sepsis in adults**

<b>I</b>	<b>Causative bacterial pathogens in sepsis</b>
1	Which bacteria are most frequently isolated from patients with sepsis in the Netherlands?
2	What are the resistance patterns of the most frequently isolated bacteria in patients with sepsis in the Netherlands?
3	Which patients are at risk for sepsis due to third-generation cephalosporin-resistant Enterobacterales (3GCR-E) or <i>P. aeruginosa</i> in the Netherlands?
<b>II</b>	<b>Empirical antibacterial therapy of sepsis</b>
4	What is the importance of appropriate empirical therapy in patients with sepsis?
5	What is the effect of double active empirical antibacterial therapy compared to monotherapy in patients with sepsis?
6	What is the optimal choice of empirical therapy in patients with sepsis in the Netherlands?
<b>III</b>	<b>Timing and duration of antibacterial therapy in sepsis</b>
7	What is the optimal timing of empirical antibacterial therapy in patients with sepsis?
8	What is the optimal duration of antibacterial treatment for sepsis?

#### IV Pharmacokinetic and pharmacodynamic considerations in sepsis

- 9 In patients with sepsis, should we recommend pharmacokinetic/pharmacodynamic dosing optimization for empirical antibacterial therapy?

318

#### 319 Methodology

320 The guideline was written according to the Appraisal of Guidelines for Research & Evaluation (AGREE)  
321 instrument.<sup>35</sup> In line with the AGREE instrument, the Guideline committee followed a guideline  
322 development process comparable to that of the Infectious Diseases Society of America (IDSA), which  
323 includes a systematic method of grading both the quality of evidence (very low, low, moderate, and  
324 high) and the strength of the recommendation (weak or strong).<sup>36</sup>

325

#### 326 Search strategy

327 In January 2017 the Surviving Sepsis Campaign International Guidelines for Management of Sepsis and  
328 Septic Shock 2016 were published.<sup>37</sup> In addition, several other international guidelines relevant to the  
329 treatment of sepsis have been published recently, including the 2017 IDSA guideline on hospital-  
330 acquired infections (HAP) and ventilator-associated infections (VAP) and the 2017 Surgical Infection  
331 Society (SIS) guideline on intra-abdominal infections.<sup>38, 39</sup> To prevent duplication of efforts we assessed  
332 the quality of these guidelines using the Appraisal of Guidelines for Research & Evaluation (AGREE) II  
333 instrument.<sup>35</sup> The overall quality of the guidelines was high. We therefore used the literature included  
334 in these guidelines for similar key questions and updated the literature since the search done by the  
335 guidelines if necessary. We subsequently assessed if the evidence, grading of the evidence and  
336 recommendations were applicable to the Dutch situation and patients with sepsis. If not, we  
337 independently graded the evidence and developed recommendations as described below.

338

339 Several SWAB or other Dutch guidelines relevant for the treatment of sepsis have been published in  
340 recent years, including the Dutch Society of Medical Microbiology (NVMM) concept guideline on *S.*  
341 *aureus* bacteraemia (2019),<sup>8</sup> the SWAB guidelines on management of community-acquired pneumonia  
342 (CAP, 2016),<sup>7, 40</sup> invasive fungal infections (2017)<sup>33</sup> and for antimicrobial stewardship (2016).<sup>41</sup> The  
343 SWAB guideline on management of complicated urinary tract infections (2013) is currently being  
344 updated.<sup>6</sup> The SWAB guideline on bacterial central nervous system infections (2012)<sup>9</sup> is older but still  
345 adequate as judged by the SWAB executive board. The same holds true for the Dutch evidence-based  
346 guideline on necrotizing soft tissue infections (2015) and the Dutch society of Dermatology and  
347 Venereal Disease (NVDV) guideline on cellulitis and erysipelas (2013).<sup>4, 5</sup> Providing different  
348 recommendations to established Dutch guidelines is not preferable as many will be updated before  
349 the next update of the SWAB sepsis guideline. Therefore, relevant findings and recommendations in  
350 the mentioned Dutch guidelines are summarized and referred to. Relevant new evidence was  
351 mentioned only when it would change practice to patients with sepsis.

352

353 For questions not covered by the mentioned guidelines, we performed a search for systematic reviews  
354 and included studies from relevant systematic reviews in PubMed, Embase and the Cochrane library.  
355 When no systematic reviews were available we performed a search for randomized controlled trials  
356 (RCT) in the same databases. Searches were either updated since the search in 2009 of the previous  
357 SWAB sepsis guideline when applicable, or performed without a date limit. Two guideline members  
358 and a clinical librarian set up the searches for systematic reviews and randomized controlled trials. The

359 search strategy included synonyms for sepsis, the relevant study design and other appropriate  
360 components of the population and intervention within the PICO question.

361

362 Studies were included on the basis of study design (RCT or systematic review), patient population,  
363 appropriate intervention and control based on the key question. Studies were included when at least  
364 50% of the patients were non-neutropenic adults with sepsis, bacteraemia or severe/complicated  
365 infection (as defined by the study conductors) or when outcomes were reported separately for these  
366 patients. We restricted to studies that included clinically relevant outcomes.<sup>42</sup> In addition we included  
367 studies reporting on the development of antibacterial drug resistance. We therefore included the  
368 following outcome measures as defined by the conductors of individual studies:

- 369 1. Mortality: short-term mortality, long-term mortality (critically important outcome measure)
- 370 2. Morbidity: failure-free days, clinical cure, treatment failure, recurrence of infection, length of  
371 ICU/hospital stay (important outcome measure)
- 372 3. Adverse consequences of therapy: superinfections with or without resistant micro-organisms  
373 (important outcome measure); other adverse events; colonisation with resistant micro-  
374 organisms

375 We did not include non-clinical, surrogate or economic outcome measures. Studies only reported in  
376 languages other than English and Dutch were excluded.

377

378 For evidence on drug resistance in the Netherlands, the guideline committee used surveillance data  
379 from 2017 in the NethMap annual report 2018.<sup>43</sup> For the update of the guideline, we updated NethMap  
380 surveillance data with data from 2024.<sup>28</sup> Reports of the European Committee on Antimicrobial  
381 Susceptibility Testing (EUCAST) guided the interpretation of susceptibility test results.<sup>44</sup>

382

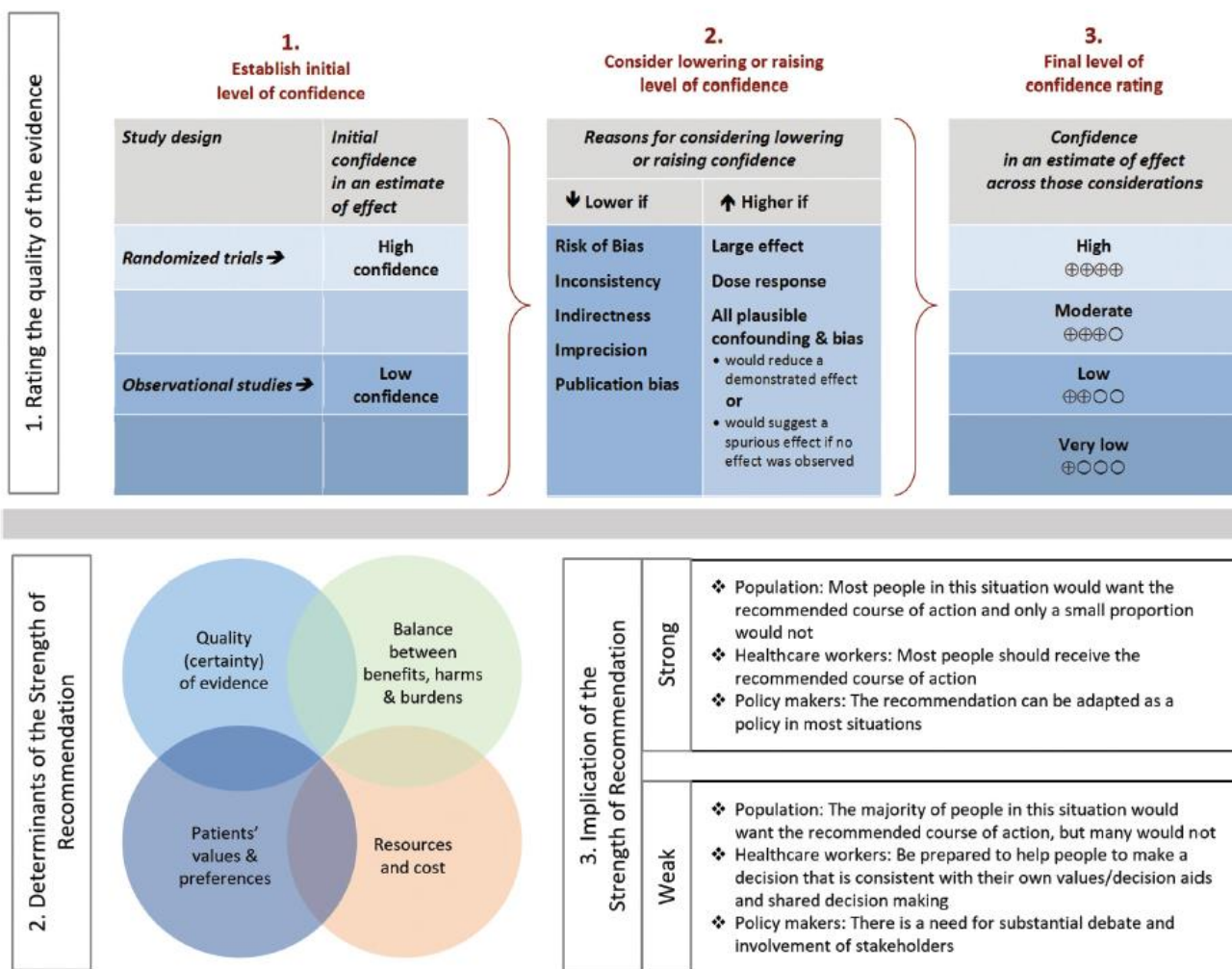
### 383 Quality assessment of literature and formulation of recommendations

384 One guideline member performed quality assessment of the literature for individual key questions,  
385 which was subsequently verified by other guideline members. The quality of evidence per outcome  
386 variable was graded according to the GRADE (Grading of Recommendations Assessment, Development  
387 and Evaluation) system, adopted by SWAB. Quality of evidence is determined by several factors, the  
388 most important of these being study design (**Figure 2**).<sup>45</sup> The remaining factors (e.g. risk of bias) can  
389 downgrade or upgrade the quality of evidence based on design. For example, an observational study  
390 with a serious risk of bias is considered to have a very low quality of evidence. Also, if the number of  
391 patients with sepsis in a study was not reported or very likely to be low, we downgraded based on  
392 indirectness. The quality of evidence is indicated with a hyphen (-) when no evidence was obtained  
393 from the literature. For readability purposes, we summarized quality of evidence for all clinically  
394 relevant outcomes in the conclusions tables.

395

396 In the final step of the process recommendations were made. The strength of recommendations was  
397 graded as Strong or Weak, taking the quality of evidence, patients' values, resources and costs, and  
398 the balance between benefits, harms and burdens into account (**Figure 2**).<sup>46</sup> The SWAB Stewardship  
399 Guideline committee and for example the WHO are of the opinion that a low quality of evidence does  
400 not necessarily lead to a weak recommendation.<sup>36, 47</sup> For example, little evidence supports sepsis  
401 removing the CVC in patients with sepsis and a suspected CVC infection, but the guideline committee  
402 nevertheless strongly recommends to do it if possible. Likewise, strong evidence for a certain  
403 intervention can sometimes nevertheless result in a weak recommendation. The reasons for the

404 guideline committee to give strong or weak recommendations are discussed for each recommendation  
 405 in the section “Other considerations”, where applicable divided into patients’ values, resources and  
 406 costs, and the balance between benefits, harms and burdens. Notably, since cost is a variable that is  
 407 highly subjective to the setting and time of research, it was difficult to translate the effects of the  
 408 included studies to the current healthcare environment in the Netherlands.  
 409



410  
 411 **Figure 2 Overview of GRADE methodology.** Approach and implications to rating the quality of  
 412 evidence and strength of recommendations using the Grading of Recommendations Assessment,  
 413 Development and Evaluation (GRADE) methodology<sup>2,3</sup>  
 414

415 When evidence could not be obtained, assigned guideline group members for the key question  
 416 proposed recommendations on the basis of opinions and experiences. These good practice statements  
 417 (GPS) were not graded using the GRADE approach and were developed according to criteria in **Table**  
 418 **2.**<sup>48</sup>  
 419

420 **Table 2. Criteria for the development of good practice statements (GPS)**<sup>48</sup>

A question applicable to any recommendation (but often violated in good practice statements)
1. Is the statement clear and actionable?

Questions particular to good practice statements
2. Is the message really necessary in regard to actual health care practice?
3. After consideration of all relevant outcomes and potential downstream consequences, will implementing the good practice statement result in large net positive consequences.
4. Is collecting and summarizing the evidence a poor use of a guideline panel's limited time and energy (opportunity cost is large)?
5. Is there a well-documented clear and explicit rationale connecting the indirect evidence?
The answers to all questions 2 - 5 should be yes to proceed with a good practice statement.

421

422 Details on the literature search and evidence summaries were published in the appendix. Drafted  
 423 recommendations per key question were presented to the complete guideline working group and  
 424 consensus reached by discussion and voting. Preparation of the guideline text was carried out by a  
 425 multidisciplinary committee consisting of experts delegated from the professional societies, including  
 426 the NIV, NVMM, NVZA, NVIC, NVvH and NVSHA. We summarized the recommendations in one figure.  
 427 The draft guideline was subsequently submitted to the members of relevant professional societies for  
 428 external review. The guideline working group will adjust the guideline according to comments in the  
 429 external review through group discussion. The final version will be presented for formal approval to  
 430 the SWAB executive board, consisting of mandated representatives of the professional societies.

431

432 **Implementation and dissemination of the guideline**

433 The formal publication of the guideline will be announced to all relevant professional societies and  
 434 presented at relevant national conferences. The recommendations in the guideline are available online  
 435 at <https://swabid.nl>.

436

437 **Conflicts of interest policy and funding**

438 The SWAB employs strict guidelines with regard to potential conflicts of interests, as described in the  
 439 SWAB Format for Guideline Development ([www.swab.nl](http://www.swab.nl)). For the development of this guideline, the  
 440 SWAB was funded by the Dutch National Institute for Public Health and the Environment (CIb-RIVM).  
 441 See **Table 3** for disclosures of the members of the Guideline committee.

442

443 **Update**

444 SWAB intends to revise their guidelines every 5 years. The potential need for earlier revisions will be  
 445 determined by the SWAB board at annual intervals, based on current literature. If necessary, the  
 446 guideline committee will be reconvened to discuss potential changes. Therefore, in 2031 or earlier if  
 447 necessary, the guideline will be re-evaluated.

448

449

450 **Table 3. Conflicts of interest of members of the SWAB sepsis guideline committee**

<b>Member</b>	<b>Potential conflict of interest</b>
E Sieswerda	None
H.I. Bax	None
J.J. Hoogerwerf	None
M.G.J. de Boer	Chair Stichting Werkgroep Antibioticabeleid; Chair COIG Infectieziekten en Immuniteit, NIV
M. Boermeester	Institutional payment for consultancy / advisory board for Johnson&Johnson, Bard, Acelity, Gore; Institutional grants Johnson&Johnson, Mylan, Bard, Acelity, LifeCell/Allergan, New Compliance
Marc Bonten	Consultant for Janssen Vaccines, (paid to UMCU); Research funding Janssen Vaccines, Immunexpress, Vedanta, (paid to UMCU); Research funding Innovative Medicines Initiative, (paid to UMCU)
D. Dekker	None
R. Gerth van Wijk	None
N. P. Juffermans	Research funding ZonMW, Sanquin, Horizon2020, CSL Behring (not related to the current guideline)
M. Kuindersma	None
P.D. van der Linden	Treasurer Stichting Werkgroep Antibioticabeleid
D. C. Melles	None
P. Pickkers	Consultancy board memberships (not related to the current guideline). Chair SepsisNet Nederland Foundation (unpaid)
J. A. Schouten	Member Wetenschappelijke Adviesraad (paid); Radboud Center Infectious Diseases ESGAP (ESCMID) secretary; SWAB member; Unrestricted educational Grant MSD
J.R. Rebel	Curriculum-, en implementatiecommissie NVSHA; Visitatiecommissie NVSHA; Member of local sepsis guideline committee
A. R. H. van Zanten	Head of ICU & Research, Ziekenhuis Gelderse Valei, Ede; Chair SKMS guideline Sepsis; Research grants Adrenoss, Nutricia, Beacon, Cardinal Health; Lectures (paid) not related to antibacterial therapy of Abbott, Baxter, BBraun, Fresenius-Kabi, Lyric, Nutricia, Nestle; The SKMS Sepsis guideline has been developed parallel to the SWAB sepsis guideline.
M.C. Kallen	None
W.P.H. van Bilsen	None
J. M. Prins	Editor in chief digital guideline antimicrobial therapy "SWAB ID", (paid to AMC); Member Wetenschappelijke Adviesraad Zorginstituut Nederland, CG (paid); Member Board Stichting de Merel (non-profit, paid to AMC)
W. J. Wiersinga	Research funding from NWO, ZonMW and Horizon2020 (not related to the current guideline); member Surviving Sepsis Guideline committee 2026.

451

452 **Definitions and abbreviations**

453 **Table 4. Definitions and abbreviations**

<b>Sepsis and infection</b>	
Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection <sup>11</sup> . For the diagnosis and non-antibiotic treatment of sepsis we refer to the Dutch guideline 'Sepsis fase 1'. <sup>3</sup>
Septic shock	A subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone <sup>10</sup> . Clinically defined as sepsis with persisting hypotension requiring vasopressors to maintain the mean arterial pressure $\geq 65$ mmHg, and with a serum lactate $>2$ mmol/L.
Bacteraemia	Also called bloodstream infection, the presence of bacteria in the blood as demonstrated by culture.
Central line-related bloodstream infection (CLABSI)	CLABSI is defined as bacteraemia / candidemia in a patient with an intravascular catheter <u>in situ</u> with <u>at least one positive blood culture</u> obtained from a <u>peripheral vein</u> , <u>clinical manifestations of infection</u> (i.e. fever, chills, and/or hypotension), and <u>no apparent source for the bloodstream infection except the catheter</u> . Bloodstream infections are considered to be associated with a central line if the line was in use during the 48-hour period before the development of the bloodstream infection. <sup>49, 50</sup>
Highly Resistant Microorganisms (HRMO)	Enterobacterales, except <i>Enterobacter cloacae</i> , were considered HRMO if they were resistant to cefotaxime/ceftriaxone and/or ceftazidime as indicator agents for the production of Extended-spectrum beta-lactamase (ESBL), or resistant to both fluoroquinolones and aminoglycosides. <i>E. cloacae</i> was considered an HRMO if resistant to both fluoroquinolones and aminoglycosides. <i>P. aeruginosa</i> was considered an HRMO if resistant to $\geq 3$ antibacterial therapy groups among fluoroquinolones, aminoglycosides, carbapenems, ceftazidime and piperacillin-tazobactam. Acinetobacter spp. were considered HRMO when resistant to imipenem or meropenem or resistance to both fluoroquinolones and aminoglycosides.**
Hospital-acquired pneumonia (HAP)	Pneumonia not present at the time of hospital admission and occurring 48 hours or more after admission <sup>38</sup>
Ventilator-associated pneumonia (VAP)	Pneumonia occurring two days or more after start invasive mechanical ventilation <sup>38</sup>
<b>Place of acquisition</b>	
Community-acquired	Occurrence of infection outside of hospital or within two days of admission, except for patients hospitalized in the past 30-90 days, residing in nursing homes, receiving haemodialysis or having long-term intravascular devices.
ICU-acquired	Acquired during stay in the ICU (two days or more)

Nosocomial	Acquired during hospital stay (two days or more after admission) or acquired within 30-90 days after hospital discharge, on haemodialysis, residing in a nursing home or having long-term intravascular devices
<b>Therapy</b>	
Antibiotic de-escalation	Changing treatment to narrow-spectrum antibiotic or stop antibiotics as soon as culture results are available. <sup>41***</sup>
Broad-spectrum therapy	Use of one or more antibacterial agents with the specific intent of broadening range of potential pathogens covered during empirical therapy
Definite therapy	Therapy targeted to a specific pathogen after microbiologic identification
Double active therapy	Antibacterial treatment with two classes of antibiotics, both targeting the known or suspected causing pathogen(s) (e.g., ceftriaxone and an aminoglycoside to target gram-negative pathogens) and with the specific purpose to accelerate pathogen clearance rather than to broaden antimicrobial coverage. Also frequently referred to as combination antibiotic therapy. Of note, the use of two antibiotics for the increased likelihood of covering the causing agent (broadening the spectrum), or for covering multiple causing agents (e.g., aerobic and anaerobic bacteria) was not included in the definition of double active therapy.
Empirical therapy	Initial therapy started in the absence of definitive microbiologic pathogen identification
2nd generation cephalosporin (2GC)	Antibacterial treatment class. In this guideline 2GC is equivalent to intravenous cefuroxime
3rd generation cephalosporin (3GC)	Antibacterial treatment class. In this guideline 3GC includes (intravenous) ceftriaxone and cefotaxime and does not include the anti-pseudomonal cephalosporin ceftazidime
3GCR-E	Enterobacterales resistant to 3GC
PK/PD	Pharmacokinetic/pharmacodynamic
SDD	Selective decontamination of the digestive tract

454 \*Sepsis criteria are derived from the 2016 Third International Consensus Definitions for Sepsis and Septic Shock  
455 (Sepsis-3).<sup>1, 10, 11</sup> In these new sepsis definition the presence of organ dysfunction is central and a requirement;  
456 until then organ dysfunction identified “severe” sepsis, a term that was abandoned in the Sepsis-3 definition.

457 \*\*HRMO definitions are, In line with Nethmap, as defined by of the Working Group on Infection Prevention (WIP,  
458 [www.rivm.nl/Onderwerpen/W/Werkgroep\\_Infectie\\_Preventie\\_WIP](http://www.rivm.nl/Onderwerpen/W/Werkgroep_Infectie_Preventie_WIP)).

459 \*\*\*Definition of antibiotic de-escalation in accordance with consensus guideline European Society of Clinical  
460 Microbiology and Infectious Diseases (ESCMID) 2019: 1. Replacing broad-spectrum antimicrobials with agents of  
461 a narrower spectrum or a lower ecological impact. or 2. Stopping components of an antimicrobial combination.

## 462 Key questions

### 463 I Causative bacterial pathogens in sepsis

464

#### 465 Introduction

466 Chapter 1 and 2 summarize the epidemiology of bacterial pathogens involved in sepsis in the  
467 Netherlands, and their resistance patterns. Chapter 3 identifies risk factors for Enterobacterales  
468 resistant to 3rd generation cephalosporins or Pseudomonas.

### 469 1. Which bacteria are most frequently isolated from patients with sepsis in the 470 Netherlands?

#### 471 Evidence summary

472 For the update of the guideline, we updated NethMap surveillance data with data from 2024 (Table  
473 5).<sup>28</sup> In addition, we added relevant results from a Dutch sepsis trial that was conducted since the  
474 previous guideline version.

#### 475 Reported pathogens in Dutch sepsis studies

476 A number of prospective studies reporting on the bacterial aetiology of sepsis in the Netherlands have  
477 been published.<sup>51-53</sup> The PHANTASi trial was an open label RCT comparing the effect of early  
478 administration of antibiotics in the ambulance to usual care in patients with sepsis (n=2672 patients;  
479 primary results are discussed in chapter 7).<sup>51</sup> Most patients had severe sepsis (57%), a minority septic  
480 shock (3.9%) and 9.5% of patients were admitted to the ICU. The most frequent suspected primary  
481 sources of sepsis were pulmonary (55%), urinary tract (22%), abdominal (6.6%) and skin or soft tissue  
482 (5.5%) infections. The remaining patients had infections at other sites (6.5%) or no infection (1.5%). In  
483 patients in which cultures were taken gram-positive pathogens were identified in 21% (staphylococci  
484 9.1%, streptococci 7.7%), gram-negative pathogens in 30% (*E. coli* 21%, other 9.6%), and fungal  
485 pathogens in 3.4% of cases.

486 The Molecular Diagnosis and Risk Stratification of Sepsis (MARS) project prospectively included almost  
487 7000 intensive care unit (ICU) patients between 2011 and 2014.<sup>52, 53</sup> In a sub-cohort of 2579 patient  
488 with sepsis, the most frequent suspected primary sources of sepsis were pulmonary (50%), abdominal  
489 (16%), bloodstream (8.9%), urinary tract (6.3%), and skin or soft tissue (4.6%) infections.<sup>32</sup> In a report  
490 of 1060 patients of the MARS project with definite or probable infection and sepsis, gram-positive  
491 pathogens were identified in 48%, gram-negative pathogens in 58% and fungal pathogens in 11% of  
492 cases.<sup>54</sup> In some sepsis episodes multiple causative pathogens were isolated. The number of patients  
493 with community-acquired versus healthcare-associated sepsis was not yet reported.

494 A retrospective cohort study from the Netherlands reported causes of sepsis in all patients in 2012  
495 hospitalized in two university hospitals with a diagnosis of sepsis.<sup>55</sup> Among 252 patients, 60% had  
496 severe sepsis or septic shock. The most common sources of sepsis were urinary tract infections (UTI;  
497 30%) and respiratory tract infections (17%). In patients with severe sepsis or septic shock, source of  
498 sepsis was predominantly intra-abdominal and the respiratory tract. *E. coli* was the most commonly  
499 isolated pathogen. These data are in line with two earlier Dutch retrospective cohort studies in which  
500 the aetiology of sepsis was described.<sup>56, 57</sup>

501 From 2022 to 2023, a cluster-randomized cross-over trial (SAGA) was conducted in nine Dutch  
502 hospitals, comparing cephalosporin monotherapy to cephalosporin plus aminoglycoside empirical  
503 therapy in adults with severe community-acquired sepsis of unknown, suspected urinary tract or  
504 abdominal origin.<sup>58</sup> Adults with National Early Warning Score (NEWS)  $\geq 5$  presenting at the emergency  
505 department were included and patients with known colonization with *P. aeruginosa* or third-  
506 generation cephalosporin-resistant Enterobacterales were excluded. The study was stopped  
507 prematurely. In 451 sepsis patients, source of sepsis was urinary tract in 49%, abdominal in 20% and  
508 unknown in 31%. A secondary analysis described probable causative pathogens (Koekenbier et al, in  
509 preparation). Probable causative pathogens were defined based on blood, deep tissue/pus, and urine  
510 cultures obtained within 48 hours of admission. Among 472 patients with community-acquired sepsis,  
511 270 (57%) had a probable causative pathogen identified. *E. coli* predominated (46%), followed by  
512 *Klebsiella* species (excluding *K. aerogenes*, 11%) and anaerobes (8%). In 3.3% of patients, *P. aeruginosa*  
513 was a probable pathogen (of which 44% was cultured from blood).

#### 514 Nethmap surveillance data from blood cultures

515 NethMap 2025 reported for 2024 36,674 blood isolates from unselected hospital departments from  
516 hospitalized patients.<sup>28</sup> The majority (91%) of the blood isolates were derived from patients in the  
517 general ward, while 9% came from ICU patients. The most frequently isolated micro-organisms from  
518 blood were: other gram-positives (36% overall, 61% of ICU blood isolates), *E. coli* (21% overall, 6% of  
519 ICU blood isolates), *S. aureus* (10% overall, 7% of ICU blood isolates), other Enterobacterales (6%  
520 overall, 4% of ICU blood isolates), *Enterococcus faecalis/faecium* (5.8% overall, 13% of ICU blood  
521 isolates) and *Klebsiella pneumoniae* (4.3% overall, 1% of ICU isolates). *P. aeruginosa* was isolated in 2%  
522 of blood cultures. Of importance, NethMap doesn't report other clinical characteristics, including the  
523 site of infection, the proportion that was community-acquired or nosocomial, the clinical significance  
524 and whether the patient suffered from sepsis. Also, it is unknown what the number of negative blood  
525 cultures was.

#### 526 Reported pathogens in sepsis due to HAP and VAP

527 In the MARS project, pathogens involved in sepsis due to HAP/VAP were *S. aureus* (17%),  
528 Enterobacterales (15%), *P. aeruginosa* (10%) and *H. influenzae* (5%) [personal communication MJMB].  
529 International data show somewhat different distributions of pathogens for sepsis due to HAP and VAP  
530 compared to the Netherlands. The IDSA guideline on HAP and VAP performed a meta-analysis of  
531 worldwide studies since 2000 on prevalence of pathogens of HAP and VAP.<sup>38</sup> For HAP, they reported a  
532 higher prevalence of non-glucose-fermenting gram-negative bacilli (19% of isolates, with  
533 *Pseudomonas* species accounting for 13% and *Acinetobacter* species accounting for 4%). For VAP the  
534 IDSA guideline reported worldwide prevalence data of VAP pathogens: *S. aureus* (20%–30%), *P.*  
535 *aeruginosa* (10%–20%), enteric gram-negative bacilli (20%–40%), and *Acinetobacter baumannii* (5%–  
536 10%). In contrast, NethMap reported 1% *Acinetobacter* species in sputum in ICU patients, suggesting  
537 that HAP/VAP due to *A. baumannii* is below 1%.<sup>43</sup> In NethMap 2025, this percentage was not reported  
538 separately for patients admitted to ICU. In patients admitted to inpatient departments (excl. intensive  
539 care units), *A. baumannii-calcoaceticus* complex was cultured 91 times (0%) in respiratory samples.<sup>28</sup>

#### 540 Reported pathogens in sepsis due to intra-abdominal infection

541 A large European study summarized causative pathogens of community-acquired and hospital-  
 542 associated complicated intra-abdominal infections (13% with sepsis).<sup>59</sup> Overall, cultured pathogens  
 543 were *E. coli* (approximately 41%), enteric anaerobes (approximately 13%, mainly *Bacteroides* spp),  
 544 other Enterobacterales (approximately 13%), *Enterococcus* species (16%) and streptococci (6.6%).  
 545 *Enterococcus* spp were cultured in 12% of community-acquired infections and 24% of hospital-  
 546 associated infections. *K. pneumoniae* and *P. aeruginosa* were more common in hospital-acquired than  
 547 in community-acquired infections. The Surgical Infection Society (SIS) guideline reported that  
 548 anaerobic micro-organisms are more prevalent for sources of infection in the distal gastrointestinal  
 549 tract compared to the proximal gastrointestinal tract.<sup>39</sup> A retrospective study from the Netherlands  
 550 reported only one bacteraemia with anaerobic bacteria among a total 80 patients with acute  
 551 cholangitis of which 46% had a positive blood culture.<sup>60</sup>

552 Reported pathogens in sepsis due to suspected CVC infection

553 A search in the ISIS-AR database identified 506 CLABSI in 2017 (see appendix for search strategy).<sup>61</sup> Of  
 554 these, CNS (56%) were the most common causative pathogen, followed by *S. aureus* (18%), gram-  
 555 negative bacteria (fermenting and non-fermenting) (13.6%) and *Enterococcus* spp (6.4%).  
 556

557 Another surveillance database (PREZIES) reported CLABSI in the Netherlands from 2012 to 2016.<sup>62</sup> The  
 558 report showed CNS (67%) as the most commonly isolated causative pathogens, followed by gram-  
 559 negative bacteria (fermenters and non-fermenters. 8.9%), *S. aureus* (6.7%), *Enterococcus faecium*  
 560 (5.4%) and *Candida albicans* (4.7%).  
 561

562 Internationally, a recent US study on CLABSI in oncology patients reported the following pathogens:  
 563 gram-negative bacteria (23.9%), CNS (16.9%), *Enterococcus* spp (16.9%), *Candida* spp (16.1%) and *S.*  
 564 *aureus* (12.4%).<sup>63</sup> A large surveillance study on nosocomial bloodstream infections reported pathogens  
 565 of more than 70,000 CLABSI.<sup>64</sup> The most common pathogens were CNS (31.3%), gram negative bacteria  
 566 (26.8), *S. aureus* (20.2%), and *Candida* species (9.0%).  
 567

568 **Conclusions**

Conclusion	Quality of evidence
A Dutch prospective study showed that in patients with sepsis and ICU admission gram-positive pathogens were isolated in 48% and gram-negative pathogens in 58% of patients	Moderate <sup>32</sup>
A Dutch randomized trial showed that in patients with community-onset sepsis gram-negative pathogens (mostly <i>E. coli</i> ) were cultured in 30% and gram-positive pathogens in 21% of patients	Moderate <sup>51</sup>
A secondary analysis of a Dutch multicenter trial (2022-2023) in patients with community-acquired sepsis of unknown, urinary tract, or abdominal origin showed <i>E. coli</i> (46%), <i>Klebsiella</i> species (excluding <i>K. aerogenes</i> , 11%) and anaerobes (8%) were most common probable pathogens.	Moderate <sup>58</sup> (Koekenbier et al, in preparation)
Dutch surveillance data from 2024 showed that the most frequently isolated micro-organisms from blood cultures were other gram-positives (36%), <i>E. coli</i> (21%) and <i>S. aureus</i> (10%)	Moderate <sup>28</sup>

A Dutch prospective study and pooled international data showed that the most frequently isolated micro-organisms in patients with sepsis due to HAP or VAP and ICU admission were <i>S. aureus</i> , Enterobacterales and <i>P. aeruginosa</i>	Moderate <sup>38</sup>
In contrast to pooled international data, Dutch surveillance data showed that <i>A. baumannii</i> is not frequently isolated in respiratory culture of hospitalized patients	Moderate <sup>28, 43</sup>
A European study showed that the most frequently isolated micro-organisms in patient with sepsis due to intra-abdominal infections were <i>E. coli</i> , enteric anaerobes, other Enterobacterales, Enterococcus species and streptococci	Very low <sup>59</sup>
Two Dutch surveillance databases showed that most frequently isolated micro-organisms in patients with CLABSI were CNS, gram-negative bacteria (fermenters and non-fermenters), <i>S. aureus</i> , <i>Enterococcus</i> spp and <i>Candida albicans</i>	Moderate <sup>61, 62</sup>

569

570 **2. What are the resistance patterns of the most frequently isolated bacteria in**  
571 **patients with sepsis in the Netherlands?**

572 **Evidence summary**

573 For the update of the guideline, we updated percentages of antibacterial drug resistance of the most  
574 frequent pathogens in blood cultures of patients in unselected departments in the Netherlands with  
575 data from 2024 (Table 5).<sup>28</sup> In addition, we added relevant culture results from the Dutch SAGA trial  
576 that was conducted since the previous guideline version and a post-hoc analysis of the Phantasi trial  
577 that was reported in the previous guideline version.<sup>51, 58, 65</sup>

578 It should be noted that resistance rates in NethMap are based on the first isolate per species per  
579 patient per year. Emergence of resistance within bacteria in individual patients, especially those  
580 patients that stay longer in the hospital and those with recurrent infections, might therefore be higher  
581 than reported here.

582 In 2024, *S. aureus* was cultured in 10% of positive blood cultures.<sup>28</sup> Of these, 1.9% was resistant to  
583 oxacillin, which was slightly higher compared to the 1% reported in the SWAB sepsis guideline 2020  
584 based on Nethmap data from 2017.<sup>27</sup>

585 Amoxicillin-clavulanic acid resistance in *E. coli* blood isolates decreased from 37% in 2017 to 31% in  
586 2024. For *K. pneumoniae* resistance increased minimally from 17% in 2017 to 18% in 2024.

587 Resistance to cephalosporins in *E. coli* increased between 2017 and 2024 according to NethMap  
588 reports. Cefuroxime resistance in *E. coli* blood isolates increased from 12% to 13%, while ceftriaxone /  
589 cefotaxime resistance increased from 6% to 9% of *E. coli* blood isolates. Ciprofloxacin resistance in *E.*  
590 *coli* isolates from blood decreased from 14% to 13% between 2017 and 2024, while gentamicin  
591 resistance increased from 4% to 5%. NethMap reported that in 2024 9% of *E. coli* blood isolates was  
592 resistant to a third generation cephalosporin and/or harboured ESBL.

593 Resistance to cephalosporins also generally increased in *K. pneumoniae*. In 2017, 14% and 10% of *K.*  
594 *pneumoniae* blood isolates were resistant to 2<sup>nd</sup> and 3<sup>rd</sup> generation cephalosporins respectively. In  
595 2024 16% of first *K. pneumoniae* blood isolates were resistant to cefuroxime, while 14% showed  
596 resistance to any third generation cephalosporin and/or harboured ESBL. In contrast, the year before  
597 (2023), 8% of *K. pneumoniae* blood isolates were resistant to a 3<sup>rd</sup> generation cephalosporin.<sup>28</sup>  
598 Ciprofloxacin resistance in *K. pneumoniae* isolates from blood remained 14% between 2017 and 2024.  
599 Gentamicin resistance increased from 5% in *K. pneumoniae* blood isolates in 2017 to 7% in 2024.

600 Occurrence of carbapenem resistance in all *E. coli* and *K. pneumoniae* isolates has remained stable  
601 between 2017 to 2024. Among all *E. coli* and *K. pneumoniae* isolates with available meropenem or  
602 imipenem MIC in 2024, 0.0% and 0.3% of isolates respectively had meropenem and/or imipenem  
603 resistance. It should be noted that carbapenem resistance in blood isolates was higher than in all  
604 isolates. Blood isolates showed carbapenem resistance in 0.1% and 0.7% for *E. coli* and *K. pneumoniae*  
605 respectively.

606 For *P. aeruginosa* small increases in resistance to ceftazidime and piperacillin-tazobactam and a small  
607 decrease in ciprofloxacin resistance has been observed. In 2017 2% of *P. aeruginosa* isolates from  
608 blood were resistant to ceftazidime, while piperacillin-tazobactam resistance was found in 5% of  
609 isolates and meropenem resistance in 1%. In 2024, these rates were 4%, 7% and 1% respectively.  
610 Reported tobramycin and ciprofloxacin resistance was 1% and 9% in 2017. In 2024, these rates were 1  
611 and 7% respectively.

612 One study within the MARS project (2011 – 2014) reported data on resistance within a subset of ICU  
613 patients with non-pneumonia derived sepsis.<sup>66</sup> Colonization or infection with resistant bacteria was  
614 based on clinical and surveillance samples obtained in the period ranging from 2 days before until 2  
615 days after ICU admission for sepsis. Percentages of resistance of specific drug-resistant bacteria in 648  
616 patients were 10% for 3rd generation cephalosporins, 8% for ciprofloxacin, 6% for gentamicin, 2% for  
617 piperacillin-tazobactam, and 0.5% for meropenem. A sub-analysis of the PHANTASi trial (2014-2016)  
618 reported culture results in 2659 patients with suspected sepsis, transported by Emergency Medical  
619 Services to 34 Dutch hospitals.<sup>65</sup> Among 1133 patients with any positive culture (43%), 12.9% had  
620 ceftriaxone-resistant pathogens. It should be noted that the positive cultures included those from  
621 respiratory tract materials, urine, wound swabs and rectal swabs and therefore may not be  
622 representative for the causative pathogen of the sepsis episode. The most common ceftriaxone-  
623 resistant organisms were *Enterococcus faecalis*, *P. aeruginosa*, and *E. coli*. Among 539 patients with  
624 bacteremia (20%), inherently ceftriaxone-resistant organisms (*Enterococcus* species, *P. aeruginosa*)  
625 accounted for approximately 8% of isolates. However, acquired resistance (e.g., ESBL-producing *E. coli*)  
626 was not reported separately.

627 The secondary analysis of the Dutch SAGA trial also assessed appropriateness of empirical  
628 cephalosporin-based treatment in adults with community-acquired sepsis of unknown, urinary tract,  
629 or abdominal origin and excluding patients known to be colonized with *P. aeruginosa* or 3rd generation  
630 cephalosporin-resistant Enterobacterales (Koekenbier et al, in preparation). Ceftriaxone susceptibility  
631 in these sepsis patients was 96% for *E. coli* and 94% for *Klebsiella* species (excl. *K. aerogenes*), with  
632 gentamicin susceptibility of 99-100%. Group 2 Enterobacterales (with inducible AmpC, n=16) were  
633 largely ceftriaxone-susceptible (13/15, 87%; 1 missing) based on in vitro susceptibility. Twenty-six  
634 probable pathogens (8%) were inherently resistant to ceftriaxone and cefuroxime: *Enterococcus*

635 species (n=13), *P. aeruginosa* (n=9), *Candida* species (n=3), and *Listeria* (n=1). In 270 patients with a  
636 probable causative pathogen, empirical treatment (including metronidazole in abdominal sepsis)  
637 would be appropriate in 83% with ceftriaxone, 73% with cefuroxime, 86% with cefuroxime plus  
638 gentamicin. When restricting the analysis of adequate empirical therapy to Enterobacterales, *S.*  
639 *aureus*/*S. lugdunensis*, haemolytic streptococci, *S. pneumoniae*, and *H. influenzae*, empirical treatment  
640 would be appropriate in 96% with ceftriaxone, 88% with cefuroxime and 99.6% with cefuroxime plus  
641 gentamicin.

CONCEPT

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**Table 5. Percentage of growth and resistance of most frequent pathogens in blood cultures of patients in unselected departments in the Netherlands in 2024**

	In blood culture	Amoxicillin-clavulanic acid <sup>1</sup>	Cefuroxime	cefotaxime/ceftriaxone/ceftazidime/esbl <sup>2</sup>	Gentamicin	Ciprofloxacin	Piperacillin-tazobactam	Cefuroxime + gentamicin	Cefuroxime + ciprofloxacin	Ceftriaxone/cefuroxime + gentamicin	Ceftriaxone/cefuroxime + ciprofloxacin
<i>E. coli</i>	21%	31%	13%	9%	5%	13%	4%	2%	7%	1.9%	6%
<i>K. pneumoniae</i>	4.3%	18%	16%	14%	7%	14%	13%	6%	11%	6%	10%
<i>P. mirabilis</i>	1.3%	7%	0.8%	0.4%	6%	10%	0.6%	0.5%	0.6%	0.2%	0.4%
<i>E. cloacae</i>	1.5%				3%	4%					
Other Enterobacterales	6%										
<i>K. oxytoca</i>	1.3%	7%	7%	3%	0.4%	1%	8%	0%	0.2%	0%	0.2%
<i>S. marcescens</i>	0.8%				2%	4%					
<i>M. morgani</i>	0.34%				5%	10%					
<i>E. aerogenes</i>	0.4%				1.5%	3%					
<i>C. freundii</i>	0.2%				3%	3%					
<i>C. koseri</i>	0.3%	3%		3%	0.8%	0.8%	3%			0.8%	0%
<i>P. aeruginosa</i>	2.2%					7%	7%				
<i>S. aureus</i>	10%	1.9%		1.9%	0.8%	2%	1.9%				
Other Gram-positives	49%										

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<sup>1</sup> According to breakpoint for oral treatment of infections originating from the urinary tract.

<sup>2</sup> According to breakpoint for indications other than meningitis (for ciprofloxacin this only applies to Enterobacterales)

647 **Conclusions**

Conclusion	Quality of evidence
A Dutch prospective study showed the following resistance patterns to causative bacteria in patients with sepsis admitted to the ICU (excluding pneumonia): 3rd generation cephalosporins 10%, ciprofloxacin 8%, gentamicin 6%, piperacillin-tazobactam 2%, and meropenem 0.5%	Moderate <sup>66</sup>
Dutch surveillance data from 2024 showed that risk of MRSA bacteraemia is low at 1.9% of all <i>S. aureus</i> bacteraemias in the Netherlands	Moderate <sup>28</sup>
Dutch surveillance data showed that in general, the risk of resistance to a third generation cephalosporin in blood cultures is increasing. In 2024, 9% of <i>E. coli</i> and 14% of <i>K. pneumoniae</i> blood isolates were resistant to 3rd generation cephalosporins and/or harboured ESBL	Moderate <sup>28</sup>
Dutch surveillance data from 2024 showed that prevalence of carbapenem resistance in all <i>E. coli</i> and <i>K. pneumoniae</i> blood isolates was 0.1% and 0.7%	Moderate <sup>28</sup>
A secondary analysis of a Dutch multicentre trial (2022-2023) in adults with community-acquired sepsis of unknown, urinary tract, or abdominal origin (excluding patients known to be colonized with <i>P. aeruginosa</i> or 3rd generation cephalosporin-resistant Enterobacterales) showed ceftriaxone susceptibility of 96% for <i>E. coli</i> and 94% for <i>Klebsiella</i> species, with gentamicin susceptibility of 99-100%. Appropriate empirical treatment for target sepsis pathogens was achieved in 96% with ceftriaxone and 99.6% with cefuroxime plus gentamicin	Moderate (Koekenbier et al, in preparation)
Dutch surveillance data on antimicrobial resistance of specific pathogens for empirical sepsis therapies are reported in <b>Table 5</b>	Moderate <sup>43</sup>

648

649

650 **3. Which patients are at risk for sepsis due to third-generation cephalosporin-**  
651 **resistant Enterobacterales (3GCR-E) or *P. aeruginosa* in the Netherlands?**

652 **Evidence summary**

653 Predictors for sepsis due to third-generation cephalosporin-resistant Enterobacterales (3GCR-E)

654 There were no systematic reviews that specifically summarized predictors for sepsis due to  
655 Enterobacterales resistant to 3rd generation cephalosporins (3GCR-E) or HRMO.

656 One systematic review summarized colonization and risk of subsequent bacteraemia with ESBL-  
657 producing Enterobacterales in patients with solid and haematological malignancies.<sup>67</sup> The analysis  
658 included ten studies, of which three European (Germany and Spain), and the majority of patients had  
659 haematological malignancies. Patients colonized in surveillance cultures (mostly at admission) were 13  
660 times more likely to develop a bacteraemia with an ESBL-producing Enterobacterales compared to  
661 patients not colonized.

662 The previous version of the SWAB sepsis guideline suggested to start empirical therapy covering HRMO  
663 in patients with known colonization with HRMO and those treated with 3<sup>rd</sup> generation cephalosporins  
664 or fluoroquinolones in the prior 30 days.<sup>29</sup> These recommendations were externally validated by  
665 Rottier et al. in a Dutch retrospective study within a tertiary hospital and a regional hospital.<sup>68</sup> The  
666 study included 9442 episodes in which blood cultures were drawn and iv antibacterial therapy was  
667 started. The authors defined positive predictive values (PPV) of the SWAB sepsis guideline  
668 recommendations to predict bacteraemia and any culture-positive infection with 3GCR-E. PPVs of prior  
669 (90 days and 1 year) colonization with 3GCR-E were 7.4% and 6.1% for predicting bacteraemia and  
670 34.4% and 28.2% for predicting any culture-positive infection with 3GCR-E. PPVs of prior (30 days)  
671 treatment with cephalosporins or fluoroquinolones were 1.3% for predicting bacteraemia and 6.9%  
672 for predicting any culture-positive infection with 3GCR-E. PPVs of both risk factors combined were  
673 1.8% for bacteraemia and 9.7% for any culture-positive infection.

674 Another study from the same research group reported on an internally validated prediction tool for  
675 *community-onset* and *hospital-onset* bacteraemia with 3GCR-E in patients suspected of serious gram-  
676 negative infections, among eight hospitals in the Netherlands from 2008 - 2010.<sup>69</sup> In this case-control  
677 study, cases included all consecutive patients with 3GCR-E bacteraemia, while controls had other  
678 infectious episodes and were matched on hospital, time and place of onset (community vs hospital).  
679 The final risk prediction model for *community-onset* 3GCR-E bacteraemia included prior (1 year)  
680 identification of 3GCR-E, suspected urinary source of bacteraemia, being immunocompromised, any  
681 prior (2 months) use of antibiotics and older age (all associated with higher risk of bacteraemia with  
682 3GCR-E). The model also included the lower respiratory tract as suspected source of bacteraemia as a  
683 factor that decreased the risk of bacteraemia with 3GCR-E. A cut-off score proposed by the authors for  
684 daily practice had 54.3% sensitivity and 87.3% specificity. For *hospital-onset* bacteraemia with 3GCR-  
685 E, the final risk prediction model included renal disease, prior (1 year) identification of 3GCR-E, any  
686 solid malignancy, signs of hypoperfusion, prior (1 month) surgical procedure, a central venous  
687 catheter, prior (2 months) use of cephalosporins, longer length of stay (associated with a higher risk of  
688 bacteraemia with 3GCR-E) and lower respiratory tract as suspected source of bacteraemia (associated  
689 with a decreased risk of bacteraemia with 3GCR-E). The proposed cut-off score for daily practice had

690 81.5% sensitivity and 73.5% specificity. Both prediction tools are currently being validated in other  
 691 hospitals worldwide with similar prevalences of 3GCR-E.<sup>70</sup>

692 One observational study outside the Netherlands externally validated a prediction tool for infection  
 693 with ESBL-producing Enterobacterales on admission.<sup>71</sup> In this study from the US, a prediction tool was  
 694 used that was developed in a previous Italian study from Tumbarello in 2011 to predict positive clinical  
 695 cultures with ESBL-producing Enterobacterales <48h of admission.<sup>72</sup> This original prediction model was  
 696 developed within a retrospective case-control study of patients from one hospital and externally  
 697 validated in a retrospective case-control study of patients from two other hospitals. The model  
 698 included prior (3 months) antibiotic therapy with beta-lactams and/or fluoroquinolones, prior (12  
 699 months) hospitalization, transfer from another healthcare facility, Charlson Comorbidity Score of ≥4,  
 700 recent (30 day) history of urinary catheterization, age ≥70 years. The US study that validated the Italian  
 701 model was a retrospective case-control study in a single hospital. Cases had a positive culture with  
 702 ESBL-producing Enterobacterales in clinical samples <48h of hospitalization and clinical signs of  
 703 infection. The number of sepsis patients and general prevalence of ESBL-producing Enterobacterales  
 704 was not reported. Most clinical cultures were urine (76%) or blood (15%). The Italian model performed  
 705 well in the US cohort, but Charlson Comorbidity Score ≥4 and age ≥70 were not significantly associated  
 706 with cases. The proposed cut-off score within the Italian study had a sensitivity of 95% and specificity  
 707 of 47% in the US study.

708 Predictors for sepsis due to *P. aeruginosa*

709 There were no systematic reviews that specifically summarized predictors for sepsis due to *P.*  
 710 *aeruginosa*. One systematic review summarized predictors of community-onset *P. aeruginosa*  
 711 bacteraemia.<sup>73</sup> Two included retrospective observational studies defined predictors in multivariate  
 712 analysis and in comparison to *E. coli* or other gram-negative bacteria bacteraemia. Predictors were  
 713 healthcare-associated infection, the presence of a urinary device or a central venous catheter, age>90,  
 714 neutropenia, presentation of septic shock and recent antibiotic use.

715 **Conclusions**

Conclusion	Quality of evidence
Pooled data in haematology/oncology patients showed that colonization (mostly on admission) with ESBL-producing Enterobacterales was associated with an increased risk of bacteraemia with ESBL-producing Enterobacterales	Very low <sup>67</sup>
In an observational study of hospitalized patients in the Netherlands with suspected serious infection, prior (1 year) colonization with Enterobacterales resistant to 3 <sup>rd</sup> generation cephalosporins (3GCR-E) had a PPV of 6.1% for bacteraemia and 28.2% for any culture-positive infection with 3GCR-E	Very low <sup>68</sup>
In an observational study of hospitalized patients in the Netherlands with suspected serious infection with gram-negative bacteria, combining prior (90 days) colonization with 3GCR-E and/or prior (30 days) treatment with cephalosporins or fluoroquinolones had a PPV of 1.8% for bacteraemia and 9.7% for any culture-positive infection with 3GCR-E	Very low <sup>68</sup>

<p>In an observational study of hospitalized patients in the Netherlands with suspected serious infection with gram-negative bacteria, an internally validated risk prediction model* had 54.3% sensitivity and 87.3% specificity for predicting <i>community-onset</i> bacteraemia with 3GCR-E</p> <p>* including prior (1 year) identification of 3GCR-E, suspected urinary source of bacteraemia, being immunocompromised, any prior (2 months) use of antibiotics, older age and the lower respiratory tract as suspected source of bacteraemia</p>	Very low <sup>69</sup>
<p>In an observational study of hospitalized patients in the Netherlands with suspected serious infection with gram-negative bacteria, an internally validated risk prediction model* had 81.5% sensitivity and 73.5% specificity for predicting <i>hospital-onset</i> bacteraemia with 3GCR-E</p> <p>* including renal disease, prior (1 year) identification of 3GCR-E, any solid malignancy, signs of hypoperfusion, prior (1 month) surgical procedure, a central venous catheter, prior (2 months) use of cephalosporins, longer length of stay and the lower respiratory tract as suspected source of bacteraemia</p>	Very low <sup>69</sup>
<p>In an observational study of hospitalized patients in the US with community-onset infections, an externally validated risk prediction model* had 95% sensitivity and 47% specificity for predicting involvement of ESBL-producing bacteria</p> <p>* including prior (3 months) antibiotic therapy with beta-lactams and/or fluoroquinolones, prior (12 months) hospitalization, transfer from another healthcare facility, Charlson Comorbidity Score of <math>\geq 4</math>, recent (30 day) history of urinary catheterization and age <math>\geq 70</math> years</p>	Very low <sup>71</sup>
<p>In two observational studies of patients with community-onset gram-negative bacteraemia, predictors for <i>P. aeruginosa</i> were healthcare-associated infection, the presence of a urinary device or a central venous catheter, age<math>&gt;90</math>, neutropenia, presentation of septic shock and recent antibiotic use</p>	Very low <sup>73</sup>

716

717 **Other considerations**

718 The optimal choice of empirical therapy for sepsis includes a risk assessment on the involvement of  
 719 3GCR-E or *P. aeruginosa* as the causative pathogen in order to start the appropriate empirical therapy  
 720 (chapter 6) and to limit use of broad-spectrum antibacterial therapy as much as possible.

721 High quality studies with externally validated prediction tools in patients with sepsis and septic shock  
 722 are currently not available. Incidence of sepsis due to 3GCR-E may differ significantly in other countries  
 723 compared to the Netherlands and hamper the generalizability of many international studies for this  
 724 guideline. The retrospective validation of the previous SWAB sepsis guideline recommendations  
 725 showed low PPVs when using both prior colonization and cephalosporin/fluoroquinolone use in  
 726 predicting serious infection with 3GCR-E. However, prior 1 year and 3 months colonization  
 727 appropriately predicted culture-positive infection with these bacteria in 28% and 34% of patients. It  
 728 should be noted that the underlying study population were patients in whom a blood culture was  
 729 drawn and iv antibiotics were started. This was reflected in the relatively low number of positive blood  
 730 cultures (18% any bacteria, 8% Enterobacterales). The question remains how the predictors would  
 731 perform in patients fulfilling sepsis or septic shock criteria and therefore a higher likelihood of  
 732 bacteraemia.<sup>74</sup> The same applies to the other study of Rottier et al. on the new proposed prediction  
 733 tool.<sup>69</sup> In addition, a considerable amount of Dutch patients with bacteraemia due to 3GCR-E were  
 734 excluded from both studies. The excluded patients developed bacteraemia after or during treatment  
 735 for another infection and may therefore have had a higher risk of bacteraemia with 3GCR-E.

736 Other reported risk prediction models for ESBL-producing Enterobacterales bacteraemia have not yet  
737 been externally validated.<sup>75-78</sup> Without external validation it is difficult to estimate the performance of  
738 these models in the Dutch situation. Also, several large epidemiological studies assessed single  
739 predictors of antimicrobial resistance in serious infections. MacFadden et al. recently showed that in  
740 patients with gram-negative bacteraemia, a prior (1 year) clinical culture with a gram-negative bacteria  
741 resistant to the drug of interest had high specificity and positive predictive value for resistance and  
742 should be a reason to choose another antibiotic.<sup>79</sup> A meta-analysis and retrospective cohort study also  
743 found high positive predictive values of previous ESBL-producing Enterobacterales (ESBL-E)  
744 colonization on the occurrence of subsequent infection due to ESBL-E and VAP due to ESBL-E  
745 respectively.<sup>80, 81</sup>

746 Based on currently available evidence, it is challenging to provide general recommendations on the  
747 risk factors that should be used for the decision to start empirical therapy in sepsis directed to HRMO.  
748 Findings are also conflicting and this is most likely due to the multifactorial nature of the risk of HRMO.  
749 For example, use of 3<sup>rd</sup> generation cephalosporins or fluoroquinolones in the previous 30 days as  
750 suggested by the previous SWAB sepsis guideline hardly improved appropriate therapy rates and was  
751 associated with unnecessary use of carbapenem.<sup>68</sup> In contrast, any use of antibiotics in the prior two  
752 months (community-onset) and use of cephalosporins in the prior two months (hospital-onset) were  
753 items in the Dutch prediction models on 3GCR-E bacteraemia.<sup>69</sup> Also, in other studies previous  
754 antibiotics were to some extent related to HRMO infection or colonization.<sup>82-84</sup> However, patients in  
755 the intensive care unit (ICU) who receive selective decontamination of the digestive tract (SDD,  
756 including a four days 3<sup>rd</sup> generation cephalosporin treatment and frequent surveillance cultures) and  
757 as a result have negative surveillance cultures, have a lower risk of bacteraemia due to HRMO.<sup>85</sup> This  
758 further underscores the complexity of developing validated and clinically useful prediction scores to  
759 help select which septic patient should get empirical therapy aimed against 3GCR-E in the Netherlands.

760  
761 The international SSC guideline does not provide specific recommendations on the decision to start  
762 empirical treatment against HRMO in patients with sepsis. The SWAB guideline committee decided  
763 that some guidance in choices would be preferable. We concluded that prior (1 year) infection or  
764 colonization is the strongest and most common risk factor predicting subsequent infection with 3GCR-  
765 E.<sup>67, 69, 80, 81</sup>

766  
767 Until high quality and externally validated prediction rules are available, the committee agreed that  
768 clinicians should take several other factors into account on an individual patient basis to decide if  
769 empirical antibacterial therapy against 3GCR-E patients with sepsis is appropriate. These include local  
770 prevalence of 3GCR-E,<sup>86</sup> whether the sepsis is hospital-acquired,<sup>69, 71, 87</sup> and to a lesser extent  
771 healthcare-associated, versus community-acquired, whether the patient had prior (2 months)  
772 treatment with antibiotics and whether or not the patient receives SDD.<sup>69, 71, 85</sup> Finally, the committee  
773 regarded the high rate of HRMO colonization in travellers and refugees from highly endemic countries  
774 such as the Indian subcontinent as another risk factor to consider in the choice of empirical treatment  
775 in patients with sepsis. As many travellers will not be colonized anymore after several months, we  
776 suggested to include three months prior travel in the individual risk assessment, especially when the  
777 patient travelled in a highly endemic country. Prevalence of HRMO per country is available online at  
778 <https://resistancemap.cddep.org/>. The committee felt that risk of 3GCR-E involvement is especially  
779 high in patients with sepsis who were recently hospitalized abroad for >24 hours. There is no strong

780 evidence to support this statement, but it is in accordance to national infection prevention guidelines  
781 on which patients to screen for HRMO.<sup>88</sup> We therefore included this as a separate suggestion. Finally,  
782 it is essential to realise the limitations of using risk factors for the decision to treat for 3GCR-E, to weigh  
783 potential risk factors against the associated risk of overtreatment and to ensure antibiotic de-  
784 escalation if possible (chapter 10).

785

786 Dutch surveillance data from 2024 revealed a concerning increase in *K. pneumoniae* blood isolates with  
787 resistance to 3rd generation cephalosporins and/or ESBL production. After declining from 10% (2017)  
788 to 8% (2023), resistance suddenly increased to 13% in 2024. Overall, 14% of *K. pneumoniae* blood  
789 isolates demonstrated resistance to 3rd generation cephalosporins or ESBL production. The cause of  
790 this sudden increase remains unknown. Carbapenem resistance was detected in 0.7% of *K.*  
791 *pneumoniae* blood isolates in 2024. For the update of this guideline, the committee discussed whether  
792 this increase in resistance should impact empirical sepsis treatment recommendations. Consensus was  
793 reached that modification of current recommendations is not yet warranted, based on the following  
794 considerations: (1) It is still a relatively rare pathogen: *K. pneumoniae* accounted for 4.3% of positive  
795 blood cultures in 2024, significantly less than *E. coli* and *S. aureus*; (2) The trend is uncertain: it remains  
796 unclear whether the current increase is temporary or permanent, given that resistance was still 8% in  
797 2023; (3) *K. pneumoniae* is often a nosocomial infection: *K. pneumoniae* bacteraemia / sepsis is  
798 hospital-acquired or healthcare-associated in a significant number of cases and would therefore often  
799 already fall under recommendations for empirical therapy in patients with a high risk of 3GCR-E; (4)  
800 Previous colonization: Some patients with 3GCR-*K. pneumoniae* sepsis will already be colonized with  
801 the isolate and would therefore fall under recommendations for empirical therapy in patients  
802 colonized with 3GCR-E. This final consideration was confirmed in a secondary analysis of the SAGA trial  
803 (2022-2023), in which 94% of (probable) causative *Klebsiella* species (excl. *K. aerogenes*) was  
804 susceptible to ceftriaxone in adults with community-acquired sepsis not previously colonised with  
805 3GCR-E. The committee has nevertheless added the suggestion to the update of the guideline to  
806 consider escalation of antimicrobial therapy in patients with persistent sepsis on 3rd generation  
807 cephalosporin treatment when a relevant *K. pneumoniae* isolate has been cultured, pending  
808 susceptibility results. In addition, the committee suggests that microbiologists and clinicians are aware  
809 of the local resistance rates, especially for *K. pneumoniae* and adjust their empirical sepsis treatment  
810 guidelines if needed.

811

812 With regards to the risk of sepsis due to *P. aeruginosa*, we found no Dutch or externally validated  
813 studies on prediction rules for sepsis or severe infections due to *P. aeruginosa*. Based on 2024  
814 Nethmap data, the a priori risk of a bloodstream infection with *P. aeruginosa* in the Netherlands is  
815 relatively low: in 2% of positive blood cultures in hospitalized patients *P. aeruginosa* was identified  
816 (chapter 2). Identified risk factors for *P. aeruginosa* are healthcare-associated infection, presence of a  
817 urinary device or a central venous catheter, extreme old age, neutropenia, presentation with septic  
818 shock and recent antibiotic use. However, the quality of this evidence is very low and no prediction  
819 tools have been designed (nor validated) in this setting. A large French prospective ICU study showed  
820 that almost all *P. aeruginosa* isolates of clinical infection were similar to isolates found in prior  
821 screening cultures.<sup>89</sup> Most clinical infections were VAP, followed by surgical site infections and  
822 bacteraemia, but numbers were low. However, in the community-acquired setting, the secondary  
823 analysis of the SAGA trial showed *P. aeruginosa* was still a probable pathogen in 3.3% of patients

824 despite not being known to be colonised with *P. aeruginosa* in the year before (Koekenbier et al, in  
 825 preparation).

826  
 827 Described risk factors for sepsis due to *P. aeruginosa* overlap with risk factors for sepsis due to 3GCR-  
 828 E to a large extent. For the Dutch clinical setting, empirical therapy for 3GCR-E is generally effective for  
 829 *P. aeruginosa* infections. Until high quality studies are available, the committee suggests to empirically  
 830 cover *P. aeruginosa* in patients with sepsis when prior (1-year) cultures showed *P. aeruginosa* (chapter  
 831 4). In addition, we suggest to cover *P. aeruginosa* in patients with sepsis due to HAP/VAP or suspected  
 832 infected CVC infection (chapter 6a). The guideline committee does not make a recommendation for or  
 833 against the empirical coverage of *P. aeruginosa* in patients with sepsis of unknown origin or with a  
 834 source other than HAP/VAP or suspected infected CVC infection when no prior cultures are available  
 835 but the above-mentioned risk factors are present. This will depend on individual patient characteristics  
 836 and local epidemiology. For recommendations on antibacterial therapy in sepsis due to 3GCR-E or *P.*  
 837 *aeruginosa*, we refer to chapter 6.

838

839 **Recommendations**

Recommendation	Strength	Quality of evidence
1. We recommend empirical therapy against 3GCR-E in patients with sepsis and prior (1 year) proven infection or colonization with 3GCR-E	Strong	Very low
2. We suggest that clinicians take into account the risk of 3GCR-E involvement in sepsis on an individual patient basis to decide if empirical antibacterial therapy against 3GCR-E is appropriate  Factors to guide this decision include local prevalence of 3GCR-E, if the infection is hospital-acquired/health-care associated versus community-acquired, prior (2 months) broad-spectrum antibiotic use, concurrent use of SDD, prior (3 months) travel to a highly endemic country (see <a href="https://resistancemap.cddep.org/">https://resistancemap.cddep.org/</a> ) and prior (2 months) hospitalization abroad	Weak	Very low
3. We suggest to consider escalation of antimicrobial therapy in patients with persistent sepsis on 3rd generation cephalosporin treatment when a relevant <i>K. pneumoniae</i> isolate has been cultured, pending susceptibility results	Weak	Very low
4. We recommend empirical therapy against <i>P. aeruginosa</i> in patients with sepsis and prior (1 year) infection or colonization with <i>P. aeruginosa</i>	Strong	Very low

840

841

## 842 **II Empirical antibacterial therapy of sepsis**

843

### 844 **Introduction**

845 The choice of empirical antibacterial treatment in sepsis depends on several factors. General factors  
846 to consider are the site of infection, the bacteria that are potentially involved and the  
847 pharmacokinetics of antibacterial agents. Other important factors are: previous culture results,  
848 whether the infection is community acquired or healthcare associated, the degree to which a patient  
849 is immunocompromised, other comorbidities and the presence of foreign material in the body. In  
850 addition, it is essential to consider the local epidemiology and resistance patterns of pathogens  
851 commonly involved in sepsis (chapter 1). In chapter 4 to 6 we summarized the evidence on empirical  
852 antibacterial therapy in patients with sepsis in general with a focus on the Netherlands. We included  
853 the following topics: importance of appropriate empirical therapy (chapter 4), empirical monotherapy  
854 versus double active therapy (chapter 5), and empirical therapy for sepsis due to the most common  
855 causes of infection when there is no suspicion of involvement of Enterobacterales resistant to 3<sup>rd</sup>  
856 generation cephalosporins (3GCR-E, chapter 6a). In that chapter we also summarized evidence and  
857 provided recommendations on empirical antibacterial therapy of sepsis and potential involvement of  
858 specific micro-organisms: patients at risk of sepsis due to 3GCR-E (chapter 6b) and patients with sepsis  
859 and risk of involvement of *S. aureus* (chapter 6c).

### 860 **4. What is the importance of appropriate empirical therapy in patients with** 861 **sepsis?**

#### 862 **Evidence summary**

##### 863 Appropriate empirical therapy in sepsis in general

864 Paul et al. performed a meta-analysis on the effect of appropriate empirical antibiotic therapy on 30-  
865 day, all-cause mortality in adults with sepsis and microbiologically documented infection including 70  
866 prospective studies.<sup>27</sup> Appropriate antibacterial therapy was defined as treatment matching in vitro  
867 susceptibility of the cultured pathogen. Inappropriate therapy was associated with increased mortality  
868 in most analyses. Among studies adjusting for comorbidity and sepsis severity, inappropriate therapy  
869 was associated with higher mortality (OR 1.60; 95% CI 1.37 to 1.86; 26 studies). Included studies had  
870 low risk of bias, but there was considerable heterogeneity and some suggestion of publication bias.

871

872 Marquet et al. performed a meta-analysis of appropriate empirical antibacterial therapy in patients  
873 with severe infections (defined as pneumonia, bacteraemia, sepsis, severe sepsis, or septic shock) on  
874 mortality, length of stay and costs.<sup>90</sup> A total of 27 high quality observational studies were included. The  
875 meta-analysis showed that appropriate in-hospital empirical antibacterial therapy was associated with  
876 reduced 30-day mortality (RR 0.71, 95% CI 0.62 - 0.82). Similar effect was found in the studies reporting  
877 in-hospital mortality (RR 0.67, 95% CI 0.56 - 0.80), but with high heterogeneity. Sensitivity analysis  
878 showed that data were robust. Inappropriate antibacterial therapy was also associated with increased  
879 costs and length of stay in some studies.

880

881 In line, another systematic review summarized the effect of inappropriate empirical therapy on  
882 mortality in 39 studies on nosocomial infections with gram-negative bacteria.<sup>91</sup> Sites of infection were  
883 respiratory, intra-abdominal, bloodstream, and urinary tract, and the majority studied patients with

884 bacteraemia. Appropriate therapy was related to susceptibility and timeliness (administration of  
885 therapy <24 to 72 hours) in 68% of studies and to susceptibility only in 20% of studies. Overall mortality  
886 was lower when receiving appropriate antibacterial therapy (OR 0.38, 95% CI 0.30-0.47), but with  
887 significant heterogeneity (65%). Similar effect estimates were found for 14-day, 30-day mortality, as  
888 well as for many subgroup analyses on overall mortality, including infections caused by *Acinetobacter*  
889 spp. and *Pseudomonas* spp. and serious gram-negative infections.

890

#### 891 Appropriate empirical therapy in sepsis due to HRMO

892 The impact of appropriate empirical therapy on severe infections due to HRMO has been assessed in  
893 observational studies only. A meta-analysis on empirical therapy for bacteraemia with ESBL-producing  
894 Enterobacterales showed a decreased risk of death with appropriate therapy (RR 0.44, 95%CI 0.44 –  
895 0.88).<sup>92</sup> The number of patients with sepsis was not reported and the analyses were not adjusted for  
896 confounders. The previously described systematic review of 191 observational studies in >70,000,  
897 mainly bacteraemic patients found that inappropriate empirical therapy was associated with higher  
898 mortality.<sup>86</sup> A meta-analysis assessing mortality in bacteraemia due to ESBL-producing  
899 Enterobacterales compared to non-ESBL-producing Enterobacterales also assessed the effect of  
900 inadequate empirical therapy on mortality.<sup>93</sup> Overall, mortality in ESBL-producing Enterobacterales  
901 bacteraemia was increased. The odds ratio decreased when adjusted for inadequate empirical therapy.

902

#### 903 Appropriate empirical therapy in sepsis due to anaerobic bacteria

904 We found no systematic reviews or RCTs assessing the effect of appropriate empirical therapy in sepsis  
905 due to anaerobic bacteria in general. Also, there are no randomized studies available on the effect of  
906 anti-anaerobic treatment in patients with sepsis due to suspected aspiration pneumonia. The 2017  
907 Surgical Infection Society (SIS) guideline on intra-abdominal infections performed a systematic  
908 literature search on appropriate empirical therapy in intra-abdominal infections.<sup>39</sup> Five studies showed  
909 that appropriate empirical therapy covering anaerobic bacteria reduced treatment failure and death  
910 in mostly complicated intra-abdominal infections. The Dutch evidence-based guideline on necrotizing  
911 soft tissue infections did not systematically search for evidence on anaerobic coverage in empirical  
912 treatment.<sup>4</sup>

913

#### 914 Appropriate empirical therapy in sepsis due to enterococci

915 In the previous SWAB sepsis guideline in 2010, evidence on the effect of empirical coverage of  
916 enterococci in patients with intra-abdominal sepsis was summarized.<sup>29</sup> Eleven RCTs in patients with  
917 complicated intra-abdominal infections showed that empirical regimens with antibiotic coverage of  
918 enterococci was not associated with a better clinical outcome than regimens without coverage of  
919 enterococci, although APACHE scores were generally low. Since then two more RCTs showed a similar  
920 outcome, i.e. no difference in outcomes between a regimen with antibiotic coverage of enterococci  
921 (tigecycline) compared to a regimen without coverage of enterococci (ceftriaxone and  
922 metronidazole).<sup>94, 95</sup> Most patients had APACHE scores < 10. The SWAB guideline on urinary tract  
923 infections (UTI) did not systematically summarize the need to cover enterococci.<sup>6</sup> We found no RCTs  
924 or systematic reviews comparing anti-enterococcal therapy in patients with sepsis and a suspected  
925 CVC infection.

926

#### 927 **Conclusions**

Conclusion	Quality of evidence
Pooled data showed a large beneficial effect of appropriate empirical antibacterial therapy on 30-day mortality, in-hospital mortality and cost in patients with severe infections	Moderate to very low <sup>27, 90</sup>
Pooled data showed that appropriate empirical antibacterial therapy reduces all-cause mortality in patients with gram-negative infections, including the subgroups with infection due to <i>Acinetobacter</i> spp. or <i>Pseudomonas</i> spp.	Very low <sup>91</sup>
Pooled observational data showed a beneficial effect of appropriate empirical antibacterial therapy reduces 30-day mortality in patients with bacteraemia with ESBL-producing Enterobacterales	Very low <sup>92</sup>
Pooled data showed that empirical anti-anaerobic therapy reduces treatment failure and mortality in patients with intra-abdominal infections	Very low <sup>39</sup>
We found no RCTs or systematic reviews on the effect of anti-anaerobic therapy in other causes of sepsis when anaerobic bacteria might be involved	-
Multiple RCTs showed that empirical anti-enterococcal therapy did not change treatment outcomes compared to no anti-enterococcal empirical therapy in patients with complicated intra-abdominal infections	Moderate <sup>29, 94, 95</sup>
We found no RCTs or systematic reviews on the effect of anti-enterococcal therapy in other causes of sepsis when <i>Enterococcus</i> spp. might be involved	-

928

929 *Other considerations*

930 The importance of appropriate empirical antibacterial therapy in patients with sepsis has been  
931 supported by systematic reviews of observational studies only. The effect has been found rather  
932 consistent and includes reduced mortality, costs and length of hospital stay. However, published  
933 studies show large heterogeneity and there is a high risk of bias due to confounding. Heterogeneity  
934 could relate to many factors, including type of infection, source control interventions, diagnostic  
935 criteria, involved bacteria, efficacy of antibacterial treatment and immune status. Methodological  
936 causes of heterogeneity could be different study designs, risks of bias, choice of statistical model and  
937 adjustment for confounding factors.

938  
939 Overall, the committee believes that the large and consistent benefits of appropriate empirical therapy  
940 in serious infections are convincing. In those patients appropriate empirical therapy generally  
941 outweighs potential harms of broader-spectrum empirical therapy, especially when resources and  
942 logistics are optimized to stop or de-escalate in an early stage when feasible. Initial empirical therapy  
943 in sepsis therefore needs to be broad enough to cover potentially involved pathogenic bacteria. This  
944 recommendation is in line with the SSC guideline which states that all likely pathogens should be  
945 covered.<sup>37</sup>

946  
947 As discussed, predicting which empirical therapy in sepsis is appropriate is complex and depends on  
948 numerous factors, including local and national antimicrobial resistance data.<sup>41</sup> The question that  
949 frequently arises is which threshold of antibiotic resistance should guide the decision to broaden the  
950 empirical antibiotic treatment. There are no studies that have validated acceptable resistance

951 prevalence cut-offs for antibacterial therapy for the empirical treatment of sepsis. Several studies have  
952 aimed to predict the likelihood of bacteraemia in general or involvement of resistant pathogens in  
953 patients with suspected infections, but cut-offs for acceptable likelihoods are generally not provided  
954 (see also chapter 2).<sup>69, 75, 76, 82, 96</sup> <sup>69, 75, 76, 82, 96</sup> In addition, no formal resistance cut-offs for appropriate  
955 empirical therapy specifically for sepsis have been defined. The annual NethMap report on surveillance  
956 data of antibiotic resistance in the Netherlands generally use <10% resistance prevalence as a cut-off  
957 for appropriateness of an antibiotic agent as empirical therapy. However, as discussed in the first  
958 chapters, NethMap data cannot be directly extrapolated to patients with sepsis. In addition, it does  
959 not take into account that in the empirical treatment setting when the causative pathogen is yet  
960 unknown, the a priori chance of resistance is lower than the resistance prevalence of single pathogens  
961 reported in national surveillance programs.<sup>68</sup> However, as discussed in chapter 3, prior (1 year)  
962 infection or colonization with a resistant gram-negative pathogen seems predictive and specific for  
963 subsequent infections with gram-negative pathogens that have similar resistance.<sup>67, 69, 79-81</sup> This has  
964 also been found for other pathogens such as MRSA.<sup>97, 98</sup> The committee therefore settled to  
965 recommend to take into account prior (1 year) relevant clinical and screenings cultures in the choice  
966 of empirical sepsis therapy in general. We cannot recommend on a cut-off for resistance prevalence in  
967 the choice of empirical antibacterial therapy. Importantly, local resistance rates of potentially involved  
968 pathogens and their resistance is one of the key factors that should be taken into account in the choice  
969 of empirical therapy of sepsis in general.

970  
971 Studies in patients with sepsis due to HRMO are very scarce. As a result, the published meta-analyses  
972 on the importance of appropriate empirical therapy in sepsis due to HRMO are often based on very  
973 low quality data according to GRADE and are mainly based on patients with bacteraemia. In contrast  
974 to the findings of the summarized meta-analyses, a Dutch retrospective study found no effect of  
975 inappropriate therapy within 24 hour of onset in ESBL bacteraemia on 30-day mortality in 232  
976 patients.<sup>99</sup> Overall, in 42% of included patients the urinary tract was the source of the ESBL  
977 bacteraemia. Separate data for 75 patients with severe sepsis or septic shock showed a trend towards  
978 increased mortality rate of inappropriate therapy within 24 hour in univariate analysis, but not in  
979 multivariate analysis. Other reports have also suggested that inappropriate therapy is not associated  
980 with increased mortality in patients with ESBL-bacteraemia with an urinary source.<sup>100, 101</sup> With only  
981 very limited data at hand, the committee suggests that until larger and prospective studies show  
982 otherwise, initial appropriate empirical therapy is of similar importance in patients with sepsis due to  
983 HRMO as in patients with sepsis in general.

984  
985 With regards to appropriate empirical therapy of anaerobic bacterial pathogens in patients with sepsis  
986 there is lack of studies, probably in part due to difficulties in culturing anaerobic bacteria. For intra-  
987 abdominal infections, a limited number of studies showed improved outcomes when anaerobic  
988 coverage is included in the empirical treatment.<sup>39</sup> In line with the SIS guideline and The Dutch evidence-  
989 based guideline on necrotizing soft tissue infections we therefore suggest anaerobic coverage in  
990 patients with sepsis and likely involvement of anaerobic pathogens.<sup>4, 39</sup> Sources of anaerobic infection  
991 include intra-abdominal infections, especially when related to the distal gastro-intestinal tract and  
992 necrotizing soft tissue infections. For cholangitis, the guideline committee follows the SIS guideline on  
993 intra-abdominal infections suggesting that anti-anaerobic therapy is generally not necessary.<sup>39, 60</sup> An  
994 exception are patients in whom a biliary-enteric anastomosis is present, in whom empirical therapy  
995 with coverage of anaerobic bacteria can be considered. The need of anaerobic coverage in aspiration

996 pneumonia remains controversial. The recent IDSA guideline on CAP summarized the evidence for  
 997 empirical treatment of anaerobic bacteria in patients with aspiration pneumonia.<sup>102</sup> Very low quality  
 998 evidence in hospitalized patients showed that anaerobic bacteria are not a frequent cause of aspiration  
 999 pneumonia. In addition, no studies were available on the added value of anaerobic treatment in  
 1000 aspiration pneumonia. The IDSA guideline on CAP committee therefore suggests not to cover  
 1001 anaerobic bacteria in aspiration pneumonia unless a long abscess or empyema is suspected. The SWAB  
 1002 sepsis guideline committee agreed to follow this suggestion for HAP and VAP, as most data comes from  
 1003 hospitalized patients.

1004  
 1005 Regarding the coverage of enterococci in the empirical therapy of sepsis, most trial data are from  
 1006 patients with complicated intra-abdominal infections. Overall, empirical treatment strategies that  
 1007 compared the inclusion or exclusion of anti-enterococcal treatment in these patients showed no  
 1008 difference in clinical outcomes.<sup>39</sup> It should be noted however that most of these studies included  
 1009 patients with community-acquired intra-abdominal infections who underwent source control, were  
 1010 not severely immunocompromised and did not have severe sepsis. There is no clear evidence to  
 1011 support or refute empirical anti-enterococcal treatment in hospital-acquired intra-abdominal  
 1012 infections, patients that have no adequate source control, the severely immunocompromised and  
 1013 patients with severe sepsis.<sup>39</sup> For enterococcal bacteraemia, retrospective data showed that  
 1014 appropriate antibacterial therapy (defined as treatment with in vitro activity for at least 6 days)  
 1015 independently reduced mortality (OR 0.33, 95% CI: 0.14 to 0.79).<sup>103</sup> Another single-centre study found  
 1016 any appropriate antibiotic as well as more days of iv amoxicillin as factors reducing mortality in  
 1017 enterococcal bacteraemia.<sup>104</sup> However, a Danish population-wide study and a Japanese cohort study  
 1018 did not find an association between initial appropriate empirical therapy for enterococci and 30-day  
 1019 mortality.<sup>105, 106</sup> In the majority of cases in the Danish population-wide study, the infection was  
 1020 hospital-acquired. The SIS guideline recommends to consider anti-enterococcal empirical therapy in  
 1021 high-risk patients with community-acquired intra-abdominal infections and those with hospital-  
 1022 acquired intra-abdominal infections, taking into account recent abdominal surgery, substantial recent  
 1023 exposure to broad spectrum antibiotics and signs of sepsis and septic shock.<sup>39</sup> The SWAB guideline on  
 1024 UTI states that it is debatable if enterococci should be covered in the empirical therapy of UTI and  
 1025 provides separate recommendations with and without covering *E. faecalis*. Based on the limited data  
 1026 available, the committee suggests not to cover enterococci in empirical therapy in patients with sepsis  
 1027 in general and most patients with community-acquired intra-abdominal infections. We suggest that  
 1028 anti-enterococcal therapy could be considered in individual patients with sepsis, e.g. those who have  
 1029 a high likelihood of enterococcal involvement based on recent relevant cultures and those with recent  
 1030 complicated intra-abdominal surgery or a suspected CVC infection and substantial exposure to broad  
 1031 spectrum antibiotics.

1032  
 1033 **Recommendations**

Recommendation	Strength	Quality of evidence
5. We recommend empirical broad-spectrum antibacterial therapy for patients presenting with sepsis to cover all pathogenic bacteria that are likely to be involved	Strong	Moderate

6. We recommend to take into account prior (1 year) resistance in relevant clinical and screenings cultures in the choice of empirical sepsis therapy	Strong	Very low
7. We recommend that empirical antibacterial therapy is guided by the local distribution of pathogens associated with sepsis and their antimicrobial susceptibilities	Strong	Very low
8. We suggest empirical antibacterial therapy for patients presenting with sepsis to cover HRMO when these are likely to be involved	Weak	Very low
9. We suggest empirical antibacterial therapy covering anaerobic bacteria for patients presenting with sepsis and intra-abdominal infections of the lower intestinal tract or necrotizing soft tissue infections	Weak	Very low
10. We generally suggest against routine empirical treatment of anaerobic bacteria in patients presenting with sepsis due to aspiration pneumonia, unless empyema or a lung abscess is suspected	Weak	Very low
11. We generally recommend against routine empirical treatment of enterococci in patients presenting with sepsis	Strong	Moderate
12. We suggest that anti-enterococcal therapy could be considered in individual patients with sepsis, e.g. those who have a high likelihood of enterococcal involvement based on recent relevant cultures and those with recent complicated intra-abdominal surgery or a suspected CVC infection and substantial exposure to broad spectrum antibiotics	Weak	Very low

1034

1035 **5. What is the effect of double active empirical antibacterial therapy compared**  
1036 **to monotherapy in patients with sepsis?**

1037 Double active empirical antibacterial therapy, also frequently referred to as combination antibiotic  
1038 therapy, is defined as antibacterial treatment with multiple classes of antibiotics, each targeting the  
1039 known or suspected causing pathogen(s) (e.g., ceftriaxone and an aminoglycoside to target gram-  
1040 negative pathogens) and with the specific purpose to accelerate pathogen clearance rather than to  
1041 broaden antimicrobial coverage. Since the previous SWAB sepsis guideline 2010, two meta-analysis  
1042 examined the effect of double active empirical antibiotic therapy compared to empirical monotherapy  
1043 in patients with sepsis,<sup>107</sup> severe sepsis or septic shock.<sup>108</sup> The Cochrane systematic review of Paul et  
1044 al. included 69 trials that compared treatment with a combination of a beta-lactam antibiotic and  
1045 aminoglycoside to beta-lactam antibiotic monotherapy in patients with sepsis.<sup>107</sup> Overall mortality in  
1046 all studies reporting on mortality was 10% (range 0 – 26%). In 23 trials the same beta-lactam was used  
1047 in the monotherapy and double active therapy group, and the meta-analysis showed no difference in  
1048 all-cause 30-day mortality (RR 0.97, 95% CI 0.73 to 1.30; 13 studies) and clinical failure in the first 30  
1049 days (RR 1.11, 95% CI 0.95 to 1.29; 20 studies). In 43 trials a broader spectrum beta-lactam was used  
1050 in the monotherapy group, and there was non-significantly reduced all-cause 30-day mortality with  
1051 monotherapy (RR 0.85, 95% CI 0.71 to 1.01) and a lower risk of clinical failure in the first 30 days (RR  
1052 0.75, 95% CI 0.67 to 0.84). Subgroup analysis of patients with sepsis due to gram-negative bacteria

1053 showed similar results, although the subgroup of patients with *P. aeruginosa* infection was too small  
1054 to draw a conclusion. There was no difference in the rate of emergence of resistance. There was a  
1055 substantial lower risk of nephrotoxicity in the monotherapy group in general (RR 0.30, 95% CI 0.23 to  
1056 0.39), but only five trials reported a once daily dosing schedule. In these trials, the RR for nephrotoxicity  
1057 was 0.17 (95% CI 0.06 – 0.53) in the monotherapy group compared to the double active therapy group  
1058 that received once daily dosing aminoglycosides.

1059  
1060 The second meta-analysis on 13 RCTs restricted the analysis of double active therapy versus  
1061 monotherapy to adult ICU patients with severe sepsis or septic shock.<sup>108</sup> SOFA scores were not  
1062 available, but >80% of included patients had APACHE II scores >20. Overall mortality was 22% (6 –  
1063 33%). RCTs compared beta-lactam monotherapy to a double active therapy of a beta-lactam with an  
1064 aminoglycoside (7 RCTs) or quinolone (3 RCTs) or one of both (1 RCT). Four RCTs used the same beta-  
1065 lactam in both groups. There was no difference in mortality at longest follow-up (RR 1.11, 95% CI 0.95  
1066 to 1.29; 11 studies, 2266 patients) or other relevant clinical outcomes such as nephrotoxicity. It was  
1067 not possible to perform the (pre-specified) subgroup analysis based on SOFA score or for patients with  
1068 shock versus patients without shock. In addition, no subgroup analysis was performed for studies with  
1069 the same beta-lactam in both groups or for patients with *P. aeruginosa* infections. The investigators  
1070 performed a trial sequential analysis showing that it is unlikely (<5%) that there would be a true relative  
1071 mortality difference between mono- and double active therapy of 20% or more.

1072  
1073 One of the included RCTs in the meta-analysis mentioned here directly above had the best external  
1074 validity for this guideline as it included patients with severe sepsis and used the same treatment in  
1075 both arms.<sup>109</sup> It compared meropenem monotherapy to meropenem and moxifloxacin double active  
1076 therapy in patients who met criteria of severe sepsis or septic shock in Germany between 2007 and  
1077 2010. Patients with recent carbapenem or quinolone treatment and those known to be colonized with  
1078 MRSA or VRE were excluded. Of the 600 patients randomized, 551 were included in the intention-to-  
1079 treat analysis. Mean SOFA and APACHE II score were 9.5 and 21.6. Overall 28-day mortality was 22.9%  
1080 at day 28. Sites of infection were pulmonary (41%), intra-abdominal (38%), urogenital (12%) and SSTI  
1081 (10%), and 50% had nosocomial sepsis. In 35% of the patients sepsis was microbiologically confirmed  
1082 and included gram-positive bacteria in 53%, gram-negative bacteria in 49% and fungi (mainly *Candida*  
1083 spp.) in 29%. *Pseudomonas* spp. was cultured in 38 patients (7% of those with microbiologically  
1084 confirmed sepsis) in any material. The study showed no difference in mean SOFA score of double active  
1085 therapy compared to monotherapy in the first 14 days after inclusion (primary endpoint). In line, there  
1086 was no difference in 28-day mortality or 90-day mortality between both groups. Emergence of bacteria  
1087 resistant to meropenem at day 21 occurred significantly more often in the monotherapy group (n=9,  
1088 5.4%) compared to the double active therapy group (n=1, 1.3%). There was no difference in overall  
1089 number of adverse events or serious adverse events. Outcomes within the subgroup of patients with  
1090 *P. aeruginosa* infection were not reported.

1091  
1092 The previous SWAB sepsis guideline described the meta-analysis of Safdar et al., which found a lower  
1093 mortality rate in patients treated with double active therapy in *P. aeruginosa* bacteraemia.<sup>110</sup> The study  
1094 had considerable limitations, such as the inclusion of treatment arms with aminoglycoside  
1095 monotherapy. A more recent meta-analysis focussed on beta-lactam monotherapy versus beta-lactam  
1096 plus aminoglycoside or fluoroquinolone in *P. aeruginosa* infections.<sup>111</sup> It included 19 studies (11  
1097 retrospective cohort studies, 8 RCTs) showing no additional effect of double active therapy on

1098 mortality, including after stratification for empirical or definite double active therapy. A subgroup  
 1099 analysis for patients with severe infections or bacteraemia showed no benefit of *definite* double active  
 1100 therapy on mortality in patients with severe infections (RR 0.96, 95% CI 0.75–1.24, heterogeneity not  
 1101 reported) or bacteraemia (RR 0.95, 95% CI 0.67–1.34). The subgroup analysis could not be performed  
 1102 for the effect of *empirical* double active therapy on mortality. There was a significant benefit of  
 1103 empirical double active therapy on clinical cure in all patients (RR 1.23, 95% CI 1.05–1.43), but this  
 1104 benefit disappeared when looking at RCTs separately. The authors reported many reasons for risk of  
 1105 bias and concluded that no solid conclusions could be drawn regarding the comparative effectiveness  
 1106 of double active versus monotherapy in *P. aeruginosa* infections. Similar findings were reported in  
 1107 another meta-analysis reporting on mortality using appropriate empirical double active therapy versus  
 1108 appropriate empirical monotherapy in *P. aeruginosa* bacteraemia.<sup>112</sup>

1109  
 1110 The Dutch guideline on *S. aureus* bacteraemia summarized evidence on double active therapy for this  
 1111 indication.<sup>8</sup> Very low quality evidence showed no additional effect of adding aminoglycosides to anti-  
 1112 staphylococcal penicillins versus anti-staphylococcal penicillin monotherapy on recurrence of  
 1113 bacteraemia and mortality. Adding aminoglycosides to anti-staphylococcal penicillins increased the  
 1114 risk of adverse events. A recent RCT on adjunctive rifampicin to anti-staphylococcal treatment (mostly  
 1115 flucloxacillin or vancomycin) in patients with *S. aureus* bacteraemia and median SOFA score of 2 did  
 1116 not show a benefit on the composite outcome of 12-week treatment failure, disease recurrence or  
 1117 death (HR 0.96, 95% CI 0.68 – 1.35).<sup>113</sup> There was a small, statistically significant reduction in disease  
 1118 recurrences in patients treated with rifampicin in a post-hoc analysis (1 versus 4%), but the clinical  
 1119 significance was unsure. Patients treated with rifampin more often suffered from adverse events and  
 1120 drug interactions (HR 1.78, 95% CI 1.20–2.65), but from a similar number of grade 3-4 adverse events  
 1121 (HR 1.12, 95% CI 0.88–1.43).

1122  
 1123 Regarding pneumonia-derived sepsis, a Cochrane systematic review on the treatment of VAP could  
 1124 not demonstrate a beneficial effect of combination antibacterial therapy compared to  
 1125 monotherapy.<sup>114</sup> Overall mortality in the four included RCTs was 20%. Antibiotic therapies evaluated  
 1126 in these patients with VAP included ceftazidime/amikacin versus meropenem, ceftazidime plus  
 1127 linezolid versus ceftobiprole, cefepime plus amikacin or levofloxacin versus cefepime and meropenem  
 1128 plus ciprofloxacin versus meropenem. There was no additional effect of double active antibiotic  
 1129 therapy compared to monotherapy for the treatment of VAP on mortality (4 RCTs, 2 of which used the  
 1130 same beta-lactam in both groups). Another meta-analysis within the IDSA guideline on HAP and VAP  
 1131 (see next chapter for more details) also could not demonstrate a beneficial effect of double active  
 1132 antibiotic therapy compared to monotherapy for the treatment of VAP with regards to mortality,  
 1133 clinical response, adverse events or acquired resistance.<sup>38</sup> We did not find appropriate meta-analyses  
 1134 on double active therapy specifically in patients with sepsis and an intra-abdominal focus.

1135  
 1136 **Conclusions**  
 1137

Conclusion	Quality of evidence
Pooled data showed no additional effect of beta-lactam + aminoglycoside double active therapy compared to the same or a different beta-lactam given	Moderate to low <sup>107</sup>

as monotherapy in patients with sepsis on all-cause mortality and clinical failure	
Pooled data showed an increased risk of clinical failure and nephrotoxicity for beta-lactam + aminoglycoside double active therapy compared to a different beta-lactam given as monotherapy in patients with sepsis	Very low <sup>107</sup>
Pooled data showed no additional effect of empirical double active therapy compared to empirical monotherapy on all-cause mortality, secondary infections and emergence of resistance in patients with sepsis and septic shock	Moderate to very low <sup>108</sup>
One randomized trial in patients with severe sepsis and septic shock showed no additional effect of double active therapy of meropenem with moxifloxacin compared to meropenem monotherapy on 28-day mortality, 90-day mortality, and adverse events at the end of study Emergence of resistance at day 21 occurred less often in the double active therapy group compared to the monotherapy group	Moderate to low <sup>109</sup>
One randomized trial in patients with <i>S. aureus</i> bacteraemia showed no additional effect of adjunctive rifampicin to anti-staphylococcal treatment (mostly flucloxacillin or vancomycin) on 12-week treatment failure, disease recurrence or death	Moderate <sup>113</sup>
One randomized trial in patients with <i>S. aureus</i> bacteraemia showed an increase in side effects of adjunctive rifampicin to anti-staphylococcal treatment (mostly flucloxacillin or vancomycin), but no difference in serious adverse events	High to moderate <sup>113</sup>
Pooled data in patients with severe <i>P. aeruginosa</i> infections showed that there is insufficient data to draw conclusions on the effect of empirical double active therapy of a beta-lactam plus aminoglycoside or fluoroquinolone compared to beta-lactam monotherapy on mortality and clinical cure	Very low <sup>107, 111, 112</sup>
Pooled data in patients with severe <i>P. aeruginosa</i> infections showed no additional effect of definite double active therapy of a beta-lactam plus aminoglycoside or fluoroquinolone compared to beta-lactam monotherapy on mortality	Very low <sup>111, 112</sup>
Pooled data in patients with VAP showed no additional effect of double active antibacterial therapy compared to monotherapy on all-cause mortality	Low <sup>38, 114</sup>

1138

1139 **Other considerations**

1140 There has been a lively and ongoing debate about double active therapy including aminoglycosides in  
1141 patients with septic shock. The SSC guideline recommends to consider double active therapy in  
1142 patients with severe sepsis and septic shock based on a weak recommendation and moderate quality  
1143 evidence. This recommendation was largely based on two studies from Kumar et al. from 2010 with  
1144 important limitations.<sup>115, 116</sup> The first was a large retrospective study that indicated that there was a  
1145 substantial survival benefit in patients with septic shock treated with double active antibacterial  
1146 therapy.<sup>116</sup> The second study was a systematic review on the effects of double active therapy in severe  
1147 sepsis and septic shock.<sup>115</sup> A total of 50 studies, including RCTs, prospective and retrospective  
1148 observational studies, were included and showed there was no overall benefit of double active therapy  
1149 (OR 0.86; 95% confidence interval, 0.71 - 1.03) with large heterogeneity. Stratification of studies with  
1150 high (>25%) mortality in the monotherapy group showed a beneficial effect of double active therapy

1151 (OR 0.54; 95% CI, 0.45 - 0.66). A subgroup analysis of critically ill patients and patients with septic shock  
1152 also showed better outcomes with double active therapy (OR 0.51; 95% CI, 0.36 - 0.72). However, the  
1153 committee finds it questionable if studies within this subgroup were comparable and relevant to the  
1154 current guideline. All studies in the mentioned subgroup were observational (7 prospective, 5  
1155 retrospective) and mostly very small. We assessed the seven included prospective studies. Three  
1156 studies included only patients with CAP or pneumococcal bacteraemia,<sup>117-119</sup> in another study the  
1157 majority of patients in the monotherapy group were treated with aminoglycoside monotherapy for  
1158 *Pseudomonas* bacteraemia,<sup>120</sup> and in one study mainly cephalosporin or aminoglycoside monotherapy  
1159 was administered for *Enterobacter* species.<sup>121</sup> The only large study on this subject which included over  
1160 2000 patients did not find any additional beneficial effect of double active therapy in gram-negative  
1161 bacteraemia.<sup>122</sup> The authors of the meta-analysis found no signs of publication bias, but other biases  
1162 were not assessed.<sup>115</sup> Of note, the SSC guideline graded the data from Kumar et al. as moderate quality  
1163 evidence based on observational studies with a strong association.<sup>37</sup> In contrast, we graded the same  
1164 evidence as very low quality evidence based on observational studies with serious risk of bias,  
1165 imprecision and serious indirectness (data not shown).

1166  
1167 A Dutch study of Ong et al. studied the effect of a short-course of adjunctive gentamicin on the  
1168 occurrence of renal failure, mortality and shock in 648 patients with severe sepsis and septic shock  
1169 admitted to two university hospital ICUs.<sup>66</sup> Hospital A had a local antibiotic guideline recommending  
1170 short-term combination treatment of a 3<sup>rd</sup> generation cephalosporin with an aminoglycoside, while in  
1171 hospital B monotherapy with a 3<sup>rd</sup> generation cephalosporin was standard of care. Combination  
1172 therapy with gentamicin (median dose 4.9 mg/kg, median duration of treatment 2 days) resulted in  
1173 more renal failure at day 14 after the start of treatment compared to monotherapy (multivariate  
1174 regression analysis: OR 1.39; 95% CI 1.00 - 1.94). There was no significant different duration of shock  
1175 (OR 1.34; 95% CI, 0.96–1.86) and 14-day mortality (OR 1.41; 95% CI, 0.94–2.12). Pre-defined sensitivity  
1176 analyses underlined the robustness of these results Confounding by indication did not seem to play a  
1177 major role as almost all patients with sepsis in hospital A received aminoglycosides irrespective of for  
1178 example renal function [personal communication JP and MJMB]. In both treatment groups and in both  
1179 ICUs 4 to 5% of patients received inappropriate empirical treatment based on in vitro antibiotic  
1180 resistance of isolated pathogens. Empirical carbapenem use was higher in the group not receiving  
1181 gentamicin (15%, versus 4% in the gentamicin group). Among the patients receiving gentamicin, 9% of  
1182 isolated pathogens was only susceptible to gentamicin.

1183  
1184 With the newer meta-analyses of Paul et al., Sjøvall et al., Vardakas et al., the landmark RCT of  
1185 Brunkhorst et al. and the described Dutch observational study of Ong et al., the guideline committee  
1186 concludes that the current evidence shows no benefits of empirical double active therapy in patients  
1187 with sepsis or septic shock on all-cause mortality.<sup>66, 107-109, 111</sup> This conclusion is in line with a recent  
1188 position statement of the IDSA.<sup>123</sup> In addition, available data in sepsis patients suggest that  
1189 aminoglycoside treatment in addition to a beta-lactam might lead to lower clinical cure rates and  
1190 higher rates of nephrotoxicity when compared to monotherapy (mostly a beta-lactam with broader  
1191 antibacterial spectrum).<sup>66, 107</sup> Studies in other patient populations are in line with these findings. A  
1192 meta-analysis of RCTs comparing therapy of a beta-lactam with an aminoglycoside to beta-lactam  
1193 monotherapy in patients with any infection showed increased risk of nephrotoxicity without any  
1194 beneficial effect regarding mortality, clinical efficacy or development of resistance.<sup>124</sup> Another  
1195 argument of using double active therapy has been with the goal to decrease the risk of antibiotic

1196 resistance development. The trial of Brunkhorst et al. showed a higher rate of resistance in the  
1197 monotherapy group of meropenem,<sup>109</sup> but this effect could not be confirmed in a meta-analysis of  
1198 RCTs reporting on emergence of antimicrobial resistance.<sup>125</sup>

1199

1200 It should be mentioned that many of the older studies included in the described meta-analyses on  
1201 double active therapy with aminoglycosides administered aminoglycosides for the complete treatment  
1202 course and in multiple daily dosing schedules, making it difficult to generalize the outcomes to the  
1203 current daily practice of once daily dosing and short course aminoglycoside treatment. Other  
1204 limitations of the available literature are that most studies only had short follow-up and did not report  
1205 on patient relevant outcomes of nephrotoxicity.<sup>108</sup> A systematic review in non-sepsis patients  
1206 summarized the toxicity of a single dose of aminoglycoside therapy among 36 studies (RCTs and  
1207 observational).<sup>126</sup> Among 24107 patients that received a single dose of aminoglycoside (mainly as  
1208 preoperative prophylaxis), 2520 developed acute kidney injury, which was usually mild and reversible.  
1209 A meta-analysis was not possible due to large heterogeneity. In contrast, the study of Ong et al. showed  
1210 clinically relevant negative outcomes already after a median aminoglycoside treatment duration of  
1211 two days in patients with sepsis.<sup>66</sup>

1212

1213 Based on summarized data the committee recommends against the use of double active therapy in  
1214 patients with sepsis, provided that the chosen single antibacterial agent is active against the most likely  
1215 pathogens involved. In contrast to the SSC guideline, we also recommend against double active therapy  
1216 in patients with severe sepsis and septic shock. It should be noted that we do not recommend against  
1217 the use of multiple antibacterial agents when the goal is to broaden the empirical treatment spectrum.

1218

1219 For sepsis due to *P. aeruginosa*, there is insufficient data from RCTs and systematic reviews to draw  
1220 conclusions on benefits and risks of empirical double active therapy. The described meta-analyses  
1221 showed no benefit of empirical double active therapy for *P. aeruginosa* infections in general, but  
1222 numbers were too small to perform a subgroup analysis for patients with sepsis or severe infections.<sup>107,</sup>  
1223 <sup>111, 112</sup> A recent retrospective observational study of patients with septic shock and documented  
1224 monomicrobial bacteraemia suggested a beneficial effect on mortality of double active empirical  
1225 therapy compared to monotherapy in a subgroup of 61 patients with *P. aeruginosa* infections.<sup>127</sup> It was  
1226 not reported with which double active empirical regimens the patients with *P. aeruginosa* were  
1227 treated. Also, there was risk of confounding by indication in the analysis. Within the overall population  
1228 of this study there was no beneficial effect of double active therapy compared to monotherapy when  
1229 a beta-lactam was used in both groups. Other more recent observational studies of double active  
1230 therapy in *P. aeruginosa* bacteraemia showed no additional effect on mortality compared to  
1231 monotherapy.<sup>128-131</sup> One of these studies found a beneficial effect on mortality of double active therapy  
1232 in the subgroup of patients treated with ciprofloxacin-based double active therapy, but not in the  
1233 subgroup treated with tobramycin-based double active therapy.<sup>130</sup> Limited evidence showed no  
1234 additional effect on mortality in patients with severe *P. aeruginosa* infections treated with definite  
1235 double active therapy. The committee concluded that although there is lack of good quality data, the  
1236 current evidence summary argues against the use of double active therapy as empirical and definite  
1237 antibacterial treatment for *P. aeruginosa* sepsis.

1238

1239 For sepsis due to *S. aureus* there is limited data suggesting that adding aminoglycosides to anti-  
1240 staphylococcal treatment has no benefits but may cause harm. Moderate quality evidence also doesn't

1241 support the addition of rifampicin in patients with sepsis. In addition, in a large retrospective study in  
 1242 964 patients, 53% of patients was treated with double active therapy and 59% of those with adjunctive  
 1243 rifampicin. Double active therapy did not affect mortality, except for the subgroup of patients with  
 1244 implanted foreign bodies or devices, which are outside the scope of this guideline.<sup>132</sup>

1245  
 1246

**Recommendations**

Recommendation	Strength	Quality of evidence
13. We recommend against routine double active empirical antibacterial therapy* for patients with sepsis or septic shock.	Strong	Moderate
14. We suggest that double active therapy is not routinely used as definite therapy for patients with sepsis due to <i>P. aeruginosa</i> infection	Weak	Very low
15. We suggest that double active therapy is not routinely used as definite therapy for patients with sepsis due to <i>S. aureus</i> infection not associated to prosthetic material	Weak	Moderate

1247 \* We defined double active antibacterial therapy as treatment with two classes of antibiotics, both targeting the  
 1248 known or suspected causing pathogen(s) (e.g., ceftriaxone and an aminoglycoside to target gram-negative  
 1249 pathogens) and with the specific purpose to accelerate pathogen clearance rather than to broaden antimicrobial  
 1250 coverage. Also frequently referred to as combination antibiotic therapy. Of note, the use of two antibiotics for  
 1251 the increased likelihood of covering the causing agent (broadening the spectrum), or for covering multiple  
 1252 causing agents (e.g., aerobic and anaerobic bacteria) was not included in the definition of double active therapy.

1253 **6. What is the optimal choice of empirical therapy in patients with sepsis in the**  
 1254 **Netherlands?**

1255 *6a. Antibacterial therapy in patients with sepsis in general*  
 1256

1257 **Evidence summary**

1258 Antibacterial therapy in patients with sepsis with unknown focus

1259 We found no RCTs that specifically focus on empirical or definite antibacterial treatment of adults with  
 1260 sepsis when there is no identified focus.

1261

1262 Antibacterial therapy in patients with sepsis due to HAP / VAP

1263 The IDSA guideline on HAP and VAP performed a systematic review of 29 RCTs on the antibacterial  
 1264 treatment of VAP.<sup>38</sup> The number of patients with sepsis was not reported, but mortality was high  
 1265 (average 21%, range 0 – 80%). There were no significant differences in mortality, clinical response,  
 1266 acquired drug resistance, or adverse events for patients treated with a cephalosporin compared to a  
 1267 non-cephalosporin or an antipseudomonal penicillin compared to a non-antipseudomonal penicillin.  
 1268 Patients treated with a carbapenem had lower mortality rates compared to patients treated with a  
 1269 non-carbapenem (RR 0.78; 95% CI, 0.65–0.95). Antibacterial treatments in the non-carbapenem group  
 1270 were a fluoroquinolone, ceftazidime, ceftazidime + an aminoglycoside, aztreonam, piperacillin-  
 1271 tazobactam or tigecycline.<sup>38</sup> The meta-analysis comparing treatment with an aminoglycoside-

1272 containing regimen to a aminoglycoside-free regimen showed lower clinical response rates in patients  
1273 treated with a aminoglycoside-containing regimen (RR 0.82; 95% CI, 0.71–0.95). The meta-analysis  
1274 comparing treatment with a quinolone-containing regimen to a quinolone-free regimen showed lower  
1275 rate of adverse events in patients treated with a quinolone-containing regimen (RR 0.88; 95% CI, 0.78–  
1276 0.99) compared to a carbapenem-based regimen or another beta-lactam-based regimen. The  
1277 previously discussed systematic review by Arthur et al.<sup>114</sup> showed higher clinical cure in the  
1278 carbapenem group compared to tigecycline,<sup>133</sup> levofloxacin,<sup>134</sup> or piperacillin-tazobactam.<sup>135</sup>

1279  
1280 The IDSA guideline additionally performed a systematic review on empirical treatment of HAP.<sup>38</sup> A  
1281 meta-analysis was only possible on four RCTs comparing a carbapenem versus piperacillin-tazobactam.  
1282 APACHE II scores were <15, 13, 13 and 23 and overall mortality rates were 2, 9, 14 and 38%. The meta-  
1283 analysis showed comparable mortality in both treatment groups (RR 0.94; 95% CI, 0.66–1.34).

1284  
1285 Antibacterial therapy in patients with sepsis due to intra-abdominal infection

1286 Several systematic reviews have been executed to analyse outcomes of different antibacterial  
1287 treatment regimens in patients with complicated intra-abdominal infections.<sup>136-140</sup> In addition, the  
1288 previously mentioned guideline of the SIS summarized evidence on the efficacy and safety of beta-  
1289 lactams in intra-abdominal infection.<sup>39</sup> For most of the included studies, the number of patients with  
1290 sepsis was not reported. Carbapenems were assessed in most (>30) RCTs, followed by a cephalosporin  
1291 plus metronidazole (21 RCTs) and piperacillin-tazobactam (14 RCTs). Overall, there were minimal  
1292 differences and no consistent differences in efficacy to comparator treatments in all these trials. One  
1293 systematic review reported a benefit of metronidazole-based therapy compared to carbapenem  
1294 treatment on mortality (OR 0.61; 95% CI: 0.37–1.00) and clinical success (OR 1.63; 95% CI: 1.08–2.45)  
1295 at the end of treatment, although the total number of events was very low.<sup>138</sup> Another systematic  
1296 review comparing clindamycin/aminoglycoside treatment to a broad-spectrum beta-lactam (with or  
1297 without beta-lactamase inhibitor) showed increased clinical cure in favour of beta-lactam treatment  
1298 (OR 0.66; 95% CI: 0.54–0.81).<sup>136</sup> Overall there was no different rate of adverse events in both treatment  
1299 groups. However, the 18 trials reporting nephrotoxicity showed a substantially increased risk of  
1300 nephrotoxicity in the clindamycin/aminoglycoside treated patients (OR 3.7; 95% CI: 2.09–6.57) and a  
1301 decreased risk of diarrhoea (OR 0.68, 95% CI: 0.46–1.00) compared to beta-lactam treatment. Two  
1302 systematic reviews compared moxifloxacin to alternative treatments in patients with complicated  
1303 intra-abdominal infections.<sup>139, 141</sup> Overall mortality was 3.8% and average APACHE II scores 7 (range 2  
1304 – 13). Overall the studies found no differences in clinical cure and mortality between groups. The  
1305 intention-to-treat analysis within the subgroup of patients with secondary peritonitis showed a non-  
1306 significant trend towards lower clinical cure than the alternative treatment group (risk difference:-  
1307 3.96%; 95% CI:- 8.54% to 0.61%).<sup>141</sup> Adverse events occurred more frequently in the moxifloxacin  
1308 group. Finally, an older systematic review comparing ciprofloxacin and metronidazole with beta-  
1309 lactam-based treatments in patients with intra-abdominal infections found that ciprofloxacin-based  
1310 treatment was associated with higher clinical cure rates than beta-lactam-based treatment (OR 1.69,  
1311 95% CI 1.20–2.39).<sup>140</sup> Average APACHE II score was reported in two studies and above 9.

1312  
1313 Removal of central venous catheter (CVC) and antibacterial therapy in patients with sepsis and  
1314 suspected CVC infection

1315 We did not find RCTs or systematic reviews that addressed the question if CVC removal alone is  
 1316 sufficient in patients with sepsis and suspected CVC infection. We also did not find RCTs or systematic  
 1317 reviews comparing antibacterial therapy choices in patients with sepsis and a suspected CVC infection.  
 1318

1319 Antibacterial therapy in patients with sepsis in general

1320 One meta-analysis compared treatment with beta-lactam/beta-lactamase inhibitors (BL/BIs) versus  
 1321 carbapenems in patients with sepsis due to several causes.<sup>142</sup> Patients were adults or children and had  
 1322 sepsis due to abdominal or pelvic infections (11 RCTs), febrile neutropenia (8) or pneumonia (7).  
 1323 Overall mortality in all studies combined was 5% (0 to 14%). The general analysis and several subgroup  
 1324 analyses showed no difference of effect on mortality, clinical failure at the end of treatment or  
 1325 development of resistance. For adverse events overall there was no difference between the study  
 1326 groups, but adverse events requiring discontinuation of the study drug occurred more often in the  
 1327 BL/BI group (1.36, 95% CI 1.03–1.79, 15 trials, 5304 patients). There was a higher risk of diarrhoea in  
 1328 the BL/BI group (RR 1.46, 95% CI 1.25–1.70, 21 trials, 6579 patients). In contrast, *Clostridium difficile*-  
 1329 associated diarrhoea (CDAD) occurred more frequently in the carbapenem group (RR 0.29, 95% CI  
 1330 0.10–0.87, 6 trials, 2002 patients). Seizures occurred significantly more frequently in the carbapenem  
 1331 group when treated with imipenem (RR 0.21, 95% CI 0.05–0.93, 4 trials, 822 patients).  
 1332

1333 **Conclusions**

Conclusion	Quality of evidence
There are no trials or systematic reviews in patients with sepsis with unknown focus available to conclude on the comparative effect of different antibiotic classes	-
Pooled data showed no additional effect of treatment with a cephalosporin compared to non-cephalosporin regimens on mortality, clinical cure, acquired resistance and adverse events in patients with sepsis due to VAP	Moderate to low <sup>38</sup>
Pooled data showed no additional effect of treatment with anti-pseudomonal penicillin compared to non-anti-pseudomonal regimens on mortality, clinical cure and adverse events in patients with sepsis due to VAP	Moderate to low <sup>38</sup>
Pooled data showed decreased mortality of treatment with a carbapenem compared to non-carbapenem regimens in patients with sepsis due to VAP. There was no additional effect on clinical cure, acquired resistance and adverse events	Moderate to low <sup>38</sup>
Pooled data showed no additional effect on mortality of treatment with a aminoglycoside-containing regimen compared to non-aminoglycoside regimens in patients with sepsis due to VAP. There were lower rates of clinical response in the aminoglycoside-based regimens and no additional effect on adverse events	Low to moderate <sup>38</sup>
Pooled data showed no additional effect on mortality, clinical cure, acquired resistance of treatment with a quinolone-containing regimen compared to non-quinolone regimens in patients with sepsis due to VAP. There was a decreased risk of adverse events with a quinolone-containing regimen	Low to moderate <sup>38</sup>
Pooled data showed no additional effect of treatment with a carbapenem compared to treatment with piperacillin-tazobactam on mortality in patients with sepsis due to HAP	Low <sup>38</sup>

Trial data showed similar effect of treatment with a cephalosporin + metronidazole, piperacillin-tazobactam or a carbapenem on clinical efficacy and safety in patients with sepsis due to intra-abdominal infection	Low <sup>39</sup>
Pooled data showed lower mortality of treatment with metronidazole plus a cephalosporin or quinolone compared to treatment with a carbapenem in patients with sepsis due to intra-abdominal infection. There was no additional effect on clinical success and adverse events	Low <sup>138</sup>
Pooled data showed increased clinical cure, a large decreased risk of nephrotoxicity and an increased risk of diarrhoea of empirical treatment with broad-spectrum beta-lactam (with or without beta-lactamase inhibitor) versus clindamycin plus aminoglycoside in patients with sepsis due to intra-abdominal infection. There was no additional effect on mortality and other adverse events	Very low to low <sup>136</sup>
Trial data showed a similar effect of monotherapy with carbapenems, tigecycline, piperacillin-tazobactam and ceftolozane-tazobactam on clinical cure in patients with sepsis due to nosocomial intra-abdominal infections	Low <sup>137</sup>
Pooled data showed increased clinical cure of treatment with ciprofloxacin plus metronidazole versus alternative treatments in patients with sepsis due to intra-abdominal infections. There was no additional effect on mortality and adverse events	Moderate to low <sup>140</sup>
Pooled data showed higher rates of adverse events of treatment with moxifloxacin versus beta-lactam based treatments in patients with sepsis due to intra-abdominal infections. There was no additional effect on clinical cure and mortality.	Low <sup>139, 141</sup>
There are no RCTs or systematic reviews comparing the effect of removal of the CVC to alternative strategies in patients with sepsis and suspected CVC infection	-
There are no RCTs or systematic reviews comparing antibiotic strategies in patients with sepsis and suspected bacterial CVC infection	-
Pooled data in patients with sepsis due to several causes showed increased risk of diarrhoea, but decreased risk of <i>Clostridium difficile</i> associated diarrhoea and seizures of empirical treatment with BL/BIs compared to carbapenem treatment. There was no additional effect on 30-day mortality, clinical cure, adverse events in general and development of resistance	Low to moderate <sup>142</sup>

1334

1335 **Other considerations**

1336 Providing evidence-based conclusions on empirical antibacterial therapy in sepsis is challenging.  
1337 Studies differ in their patient populations (severity of infection, source of infection, comorbidities,  
1338 availability of culture results, local antimicrobial resistance and MIC of involved bacteria), interventions  
1339 (dosing, additional antibacterial therapy, source control, timing of treatment) and outcomes (timing,  
1340 definition, outcome assessment). In particular, antimicrobial resistance is much lower in the  
1341 Netherlands compared to other countries and the number of Dutch patients in included trials is limited.  
1342 Another important consideration is that most trials and meta-analyses were not powered for  
1343 conclusions on the occurrence of adverse events including nephrotoxicity and the development of  
1344 antimicrobial resistance.

1345

1346 Most trials in patients with severe infections used cephalosporins, carbapenems, piperacillin-  
1347 tazobactam and some fluoroquinolones, but outcomes in general did not consistently suggest that one  
1348 of these classes of antibiotics is considerably more effective than others in patients with sepsis. Within  
1349 the summarized evidence based on trials and meta-analyses, aminoglycoside-based regimens for  
1350 sepsis due to HAP or VAP were associated with lower rates of clinical response.<sup>38</sup> For sepsis due to  
1351 intra-abdominal infections aminoglycoside monotherapy for the aerobic gram-negative pathogens was  
1352 less effective than beta-lactam treatment.<sup>136, 143</sup> The SSC guideline does not provide detailed  
1353 recommendations on the choice of empirical therapy in patients with sepsis, but they do state that in  
1354 the majority of patients with sepsis a broad-spectrum beta-lactam is most appropriate.<sup>37</sup>

1355  
1356 It is difficult to draw conclusions on aminoglycoside efficacy and toxicity for patients with sepsis.  
1357 Almost all trials available combined aminoglycosides with other antibiotics and were therefore  
1358 summarized and discussed in the chapter on double active therapy with aminoglycosides (chapter 5).  
1359 It was obvious from the described Dutch study by Ong et al that including aminoglycosides in the  
1360 empirical treatment of sepsis is carbapenem-sparing, but conversely leads to a significant number of  
1361 patients who are essentially treated with aminoglycoside monotherapy due to resistance to the beta-  
1362 lactam agent.<sup>66</sup> Aminoglycoside monotherapy is generally not considered appropriate empirical  
1363 therapy for sepsis not originating from the urinary tract, although also on this topic there is lack of  
1364 data.<sup>144</sup>

1365  
1366 The committee concluded that based on the current data about efficacy and safety of beta-lactams,  
1367 the experience with beta-lactams and the large number of trials using a beta-lactam, beta-lactams are  
1368 most appropriate as empirical and definite therapy in the majority of patients with sepsis.

1369  
1370 Based on the available literature, fluoroquinolones are acceptable alternatives when the risk of  
1371 fluoroquinolone resistance is considered low. However, clinicians should be aware that use of  
1372 fluoroquinolones has significant disadvantages regarding toxicity and development of resistance.<sup>145-148</sup>  
1373 In the discussions on aminoglycoside-based treatment, several committee members had concerns  
1374 about aminoglycoside efficacy and adverse events, especially in patients with pre-existing impaired  
1375 renal function. In contrast, aminoglycoside-based treatment is current practice for empirical sepsis  
1376 treatment in many hospitals as a carbapenem-sparing strategy. The committee settled that current  
1377 (lack of) evidence supports *short-term* (i.e. maximum of two days) aminoglycoside treatment added to  
1378 a beta-lactam agent in patients with sepsis with the only purpose of increasing the empirical  
1379 antibacterial spectrum of activity until susceptibility results are available. This strategy is therefore  
1380 mainly applicable to gram-negative bacteria such as 3GCR-E or *P. aeruginosa* (chapter 6b).

1381  
1382 There is no clear evidence-based guidance on how to define appropriate empirical therapy (chapter 4)  
1383 and it is difficult to predict a priori risk of the involved pathogen in patients with sepsis (chapter 3).  
1384 Early detection of the pathogen combined with direct guidance from the clinical microbiology  
1385 laboratory on choice of therapy could therefore be an important strategy to reduce inappropriate  
1386 empirical therapy and unnecessary broad-spectrum antibiotics in patients with sepsis.<sup>149</sup> Potential  
1387 interventions supporting this goal are improving the appropriate collection of clinical specimens,  
1388 decreasing time from collection of specimens to arrival in the microbiology lab, implementing rapid  
1389 pathogen identification and antimicrobial susceptibility testing techniques.<sup>150, 151</sup> However, studies on  
1390 efficacy of antimicrobial stewardship interventions in patients with sepsis are lacking.<sup>152, 153</sup> Although

1391 diagnosis of sepsis is no part of this guideline, the committee believes that optimizing early  
1392 identification of the involved pathogen is an important tool to improve early appropriate empirical  
1393 therapy and decrease unnecessarily broad-spectrum antibiotics in patients with sepsis. We therefore  
1394 suggest that local antimicrobial stewardship programs incorporate improvement of early diagnosis and  
1395 reporting of pathogens and susceptibility in patients with sepsis.

1396

1397 In current clinical practice the choice of empirical antibacterial treatment of sepsis differs considerably  
1398 between hospitals, e.g., a third generation cephalosporin, piperacillin-tazobactam, a combination of a  
1399 second/third generation cephalosporin with short-term aminoglycoside treatment, a combination of  
1400 a second or third generation cephalosporin with a fluoroquinolone, or a carbapenem. The final choice  
1401 is therefore dictated by the likelihood of involvement of a resistant causative pathogen, by the desire  
1402 to avoid the use of third-generation cephalosporins, fluoroquinolones and/or carbapenems from an  
1403 antibiotic stewardship perspective and by risks of toxicity and other potential adverse events for the  
1404 patient.

1405 We therefore cannot provide strong recommendations on the best empirical treatment in sepsis based  
1406 on the currently available literature. We found only subtle differences between strategies in clinical  
1407 outcomes in studies that were frequently not generalizable to the Dutch clinical setting. Consequently,  
1408 the committee provided pragmatic suggestions for empirical treatment choices in patients with sepsis  
1409 based on current evidence, reported national resistance rates, the antibiotic stewardship perspective,  
1410 PK/PD considerations and risk of adverse events. Multiple options are more or less equivalent as long  
1411 as the empirical treatment is appropriate in covering the most likely pathogens. All strategies have  
1412 advantages and disadvantages depending on the three main perspectives (likelihood of optimally  
1413 targeting the right pathogen, antimicrobial stewardship, risk of adverse events). For recommendations  
1414 on empirical therapy of patients with sepsis, we used the following considerations. First, we defined  
1415 the most important pathogens that should be treated in patients with specific clinical syndromes, using  
1416 the data described in chapter 1 and including pharmacodynamics/pharmacokinetic considerations  
1417 (PK/PD, chapter 10). We subsequently defined which empirical treatment options would be  
1418 appropriate based on the national resistance data in blood culture pathogens, described in chapter 2  
1419 and the risk of involvement of 3GC-E, as described in chapter 3. We then defined alternative  
1420 treatments with larger disadvantages based on resistance, PK/PD, antimicrobial stewardship, toxicity  
1421 or other reasons. As an example, based on these considerations the committee considered amoxicillin-  
1422 clavulanic acid plus an aminoglycoside less appropriate empirical therapy for sepsis, based on the  
1423 combination of high resistance rates of Enterobacterales for amoxicillin-clavulanic acid, concerns  
1424 about efficacy and toxicity on aminoglycosides and PK/PD considerations of both amoxicillin-clavulanic  
1425 acid and aminoglycosides.

1426

1427 Hospitals could consider alternative empirical treatment options guided by local resistance rates or  
1428 when patients do not (yet) qualify for sepsis according to the sepsis-3 criteria.<sup>1</sup> Although this guideline  
1429 is intended for patients with sepsis, in reality the recommendations are frequently used for any patient  
1430 in which blood cultures are taken and iv antibiotic therapy is considered. We would like to underscore  
1431 that those patients are formally outside the scope of this guideline. For those patients, higher chances  
1432 of resistance might be accepted as our evidence summery on the need of appropriateness of empirical  
1433 therapy (chapter 4) was only focussed on patients with sepsis.

1434

1435 In the current chapter 6a, recommendations are listed for sepsis patients at low risk of 3GCR-E (i.e. no  
1436 previous infection or colonization with 3GCR-E and a low estimated risk of 3GCR-E involvement. See  
1437 chapter 3, recommendations 1 and 2). Alternative treatment strategies are provided including in  
1438 patients with increased likelihood of involvement of *P. aeruginosa* (chapter 3, recommendation 3) or  
1439 enterococci (chapter 4, recommendation 11). In chapter 6b, empirical treatment recommendations  
1440 are provided for patients with sepsis at increased or high risk of involvement of 3GCR-E. In chapter 6c,  
1441 we provided additional recommendations on empirical therapy in patients with sepsis at increased risk  
1442 of *S. aureus* involvement. Recommendations are summarized in **Figure 1** (Summary).

1443  
1444 For definite treatment, we also refer to chapter 9 on duration of therapy in sepsis. Finally, it should be  
1445 noted that for empirical sepsis therapy PK/PD considerations apply (chapter 10).

#### 1446 1447 Sepsis in general

1448 For sepsis in general or no obvious source of infection and low estimated risk of 3GCR-E or *P.*  
1449 *aeruginosa* involvement, the committee agreed that the antibacterial spectrum should include *S.*  
1450 *aureus*, *E. coli* and haemolytic streptococci. The committee prefers a 3rd generation cephalosporin.  
1451 Alternative empirical choices are listed in **Table 6**.

#### 1452 1453 Sepsis due to CAP

1454 For empirical treatment of sepsis due to CAP, we refer to the 2016 SWAB guideline on CAP.<sup>40</sup>  
1455

#### 1456 Sepsis due to HAP and VAP

1457 For sepsis due to HAP and VAP the antibacterial spectrum should include *S. aureus*, Enterobacterales,  
1458 *P. aeruginosa* and *H. influenzae*. It should be noted that in the Netherlands the prevalence of VAP is  
1459 thought to be lower compared to other countries due to the frequent use of SDD in Dutch ICU patients.  
1460 In addition, in most patients with VAP the most likely pathogen and its resistance are known because  
1461 of the frequent surveillance cultures of the respiratory tract in patients on SDD. The number of patients  
1462 that need empirical therapy due to VAP will therefore be low. For sepsis due to HAP or VAP in patients  
1463 with unknown surveillance cultures or those not on SDD, we recommend a 2<sup>nd</sup> or 3rd generation  
1464 cephalosporin plus high dose ciprofloxacin or piperacillin-tazobactam as empirical treatment.  
1465 Alternative empirical treatment options are listed in **Table 6**. As discussed in chapter 4, we generally  
1466 suggest against routine empirical treatment of anaerobic bacteria in patients with sepsis due to  
1467 aspiration pneumonia, unless empyema or a lung abscess is suspected.

#### 1468 1469 Sepsis due to UTI

1470 For empirical treatment of sepsis due to UTI, we refer to the SWAB guideline on complicated UTI.<sup>6</sup> The  
1471 2013 guideline is currently being updated.

#### 1472 1473 Sepsis due to cholangitis

1474 For sepsis due to cholangitis, empirical treatment should have activity primarily against *E. coli* and to a  
1475 lesser extent other Enterobacterales. Anaerobic coverage is suggested for patients with cholangitis  
1476 and biliary-enteric anastomosis (see chapter 4). The guideline committee therefore recommends a 3rd  
1477 generation cephalosporin and the addition of metronidazole for patients with biliary-enteric  
1478 anastomosis. Alternative treatments are listed in **Table 6**.

1479

1480 Sepsis due to intra-abdominal infections

1481 For sepsis due to other intra-abdominal infections empirical treatment should have activity against *E.*  
1482 *coli*, streptococci, anaerobes including *Bacteroides* spp and other Enterobacterales. The committee  
1483 therefore recommends a 3rd generation cephalosporin plus metronidazole. Alternative treatments  
1484 are listed in **Table 6**.

1485 Sepsis due to skin and soft tissue infection

1486 For empirical treatment of sepsis due to skin and soft tissue infection we refer to the NVDV guideline  
1487 on cellulitis and erysipelas (2013) and the Dutch evidence-based guideline on necrotizing soft tissue  
1488 infections.<sup>4, 5</sup>

1489 Sepsis due to suspected CVC infection

1490 For sepsis due to suspected CVC infection there is lack of high quality data. The previous SWAB sepsis  
1491 guideline did not provide general recommendations on catheter removal or empirical therapy for  
1492 patients with sepsis and suspected CVC infection.<sup>29</sup> The IDSA and SSC guidelines provided strong  
1493 recommendations on the prompt removal of the line in the settings of sepsis, hemodynamic instability,  
1494 endocarditis or evidence of metastatic infection, persistent bacteraemia after 72 hours of antibacterial  
1495 therapy or infections due to *S. aureus*, *P. aeruginosa*, fungi or mycobacteria.<sup>37, 154</sup> There is no high  
1496 quality data to support this recommendations, but the committee agreed on the assumption that  
1497 retaining a CVC in patients with suspected CVC infection under the mentioned circumstances is likely  
1498 similar to absence of source control with potential increased risk of adverse outcomes. We therefore  
1499 recommend prompt CVC removal in patients with suspected CVC infection and sepsis or septic shock.

1500  
1501 Chapter 1 showed that in the Netherlands the most common pathogens of CLABSI are CNS, which  
1502 rarely cause complicated infection in patients without prosthetic valves or other intravascular  
1503 prosthetic material. In the setting of uncomplicated CLABSI with CNS and removal of the central line,  
1504 antibiotic treatment is therefore commonly withheld in The Netherlands. The committee agreed that  
1505 empirical therapy should cover *S. aureus* and gram-negative bacteria including *P. aeruginosa* in  
1506 patients with sepsis and suspected CVC infection. We suggest several equivalent treatment options in  
1507 **Table 6**.

1508  
1509 In contrast to pooled international data, Dutch surveillance data showed that Enterococci occur in less  
1510 than 6 % as causative pathogens of suspected CVC infections. Based on chapter 4 and in line with the  
1511 IDSA guideline we agreed to suggest against empirical treatment of enterococci, unless there is a very  
1512 high suspicion of involvement in individual cases based on recent cultures. The same holds true for the  
1513 empirical coverage of CNS for CVC associated sepsis. An evidence summary on the question whether  
1514 patients with intravascular prosthetic material and sepsis due to suspected CVC infection should  
1515 receive empirical treatment covering Enterococci and CNS in order to prevent secondary intravascular  
1516 prosthetic material infection was outside the scope of this guideline. However, the committee agreed  
1517 that a vancomycin-based treatment could be considered in those patients and is suggested as an  
1518 alternative in **Table 6**.

1519  
1520 It should be noted that treatment of infected long-term catheters such as Hickman, Port-a-cath,  
1521 Broviac and dialysis catheters are not covered in this guideline. Regarding the need for empirical use  
1522 of an echinocandin in patients with CVC associated sepsis, the committee refers to the SWAB  
1523 guidelines for the Management of Invasive Fungal Infections.<sup>33</sup>

1524 **Sepsis and reported penicillin allergy**  
 1525 The SWAB sepsis guidelines 2020 included a chapter with recommendations for patients with sepsis  
 1526 and suspected penicillin allergy. In the 2026 update, we refer to the recommendations in the 2022  
 1527 SWAB guideline for the approach to suspected Antibiotic Allergy.<sup>2</sup>  
 1528  
 1529

**Recommendations**

Recommendation	Strength	Quality of evidence
16. In patients with sepsis, we generally recommend using a beta-lactam antibiotic covering the most likely involved pathogens	Strong	Moderate
17. In patients with sepsis in general / with no obvious source of infection, we suggest a 3rd generation cephalosporin (3GC). Alternative empirical treatment strategies are listed in <b>Table 6</b>	Weak	Low
18. In patients with sepsis due to HAP or VAP, we suggest that there are equivalent empirical treatment strategies, listed in <b>Table 6</b>	Weak	Low
19. In patients with sepsis due to cholangitis, we suggest a 3GC. Alternative empirical treatment strategies are listed in <b>Table 6</b>	Weak	Low
20. In patients with sepsis due to intra-abdominal infection, we suggest a combination of a 3GC with metronidazole. Alternative empirical treatment strategies are listed in <b>Table 6</b>	Weak	Low
21. In patients with sepsis and a suspected CVC infection*, we recommend prompt removal of the line	Strong	GPS
22. In patients with sepsis and suspected CVC infection, we suggest empirical treatment with a 3GC** with gentamicin or high dose ciprofloxacin Alternative treatment strategies are listed in <b>Table 6</b>	Weak	GPS
23. For the empirical treatment of sepsis due to UTI, CAP and SSSI's and for patients with sepsis and suspected antibiotic allergy, we refer to other guidelines <sup>2, 4-7</sup>		

1530 \* Recommendations for sepsis due to suspected long-term CVC's were not included in this guideline  
 1531 \*\* 3GC may be given in high dose for more optimal PK/PD for *S. aureus* infections in accordance to EUCAST

1532 **Table 6. Alternative empirical treatment strategies in sepsis and low estimated risk of involvement of 3GCR-E**

Source	Choice	Empirical treatment strategy	Advantages	Disadvantages	Note
Unknown	1 <sup>st</sup>	3GC	Relatively small spectrum Low risk of adverse events Only beta-lactam component of therapy	Potentially suboptimal <i>S. aureus</i> PK/PD	High dose 3GC optional when there is a higher likelihood of <i>S. aureus</i> involvement
	Alternative	Piperacillin-tazobactam	Spectrum includes <i>E. faecalis</i> anaerobic bacteria and <i>P. aeruginosa</i> Only beta-lactam component of therapy	Broader antibacterial spectrum compared to 1 <sup>st</sup> choice Prolonged or continuous infusion strongly recommended	Optional when there is a higher likelihood of anaerobic, <i>P. aeruginosa</i> or enterococcal involvement
	Alternative	2GC plus high dose ciprofloxacin or an aminoglycoside	Spectrum includes <i>P. aeruginosa</i> Potentially better <i>S. aureus</i> PK/PD of beta-lactam component	Potentially less optimal Enterobacterales PK/PD of beta-lactam component Potentially higher risk of adverse events compared to 1 <sup>st</sup> choice TDM and max 2 day treatment for aminoglycoside	Optional when there is a higher likelihood of <i>S. aureus</i> infection or <i>P. aeruginosa</i> involvement
<b>HAP or VAP</b>	1 <sup>st</sup>	3GC plus high dose ciprofloxacin	Spectrum includes <i>P. aeruginosa</i> . Potentially better Enterobacterales PK/PD of beta-lactam component (compared to 2GC)	No anaerobic coverage. Potentially less optimal <i>S. aureus</i> PK/PD of beta-lactam component (compared to 2GC)	
	1 <sup>st</sup>	Piperacillin-tazobactam	Spectrum includes <i>P. aeruginosa</i> and anaerobic bacteria Only beta-lactam component of therapy	Broader antibacterial spectrum	
	1 <sup>st</sup>	2GC plus high dose ciprofloxacin	Spectrum includes <i>P. aeruginosa</i> . Potentially better <i>S. aureus</i> PK/PD of beta-lactam component (compared to 3GC)	No anaerobic coverage. Potentially less optimal Enterobacterales PK/PD of beta-lactam component (compared to 3GC)	

<b>Cholangitis</b>	1st	3GC	Relatively small spectrum Low risk of adverse events Only beta-lactam component of therapy	No anaerobic or enterococcal coverage.	Addition of metronidazole in patients with sepsis due to cholangitis who have biliary-enteric anastomosis
	Alternative	Piperacillin-tazobactam	Spectrum includes <i>E. faecalis</i> , anaerobic bacteria and <i>P. aeruginosa</i>	Broader antibacterial spectrum Prolonged or continuous infusion strongly recommended	Optional when there is a higher likelihood of anaerobic, enterococcal or <i>P. aeruginosa</i> involvement  <u>Alternative treatment</u> option to 3GC plus metronidazole in patients with sepsis due to cholangitis who have biliary-enteric anastomosis
	Alternative	2GC/3GC plus high dose ciprofloxacin or an aminoglycoside	Spectrum includes <i>P. aeruginosa</i>	No anaerobic coverage Potentially higher risk of adverse events TDM and max 2 day treatment for aminoglycoside	Optional when there is a higher likelihood of <i>P. aeruginosa</i> involvement Addition of metronidazole in patients with sepsis due to cholangitis who have biliary-enteric anastomosis
<b>Intra-abdominal infection</b>	1st	3GC plus metronidazole	Relatively small spectrum Low risk of adverse events Only beta-lactam component of therapy		
	Alternative	Piperacillin-tazobactam	Spectrum includes <i>E. faecalis</i> and <i>P. aeruginosa</i>	Broader antibacterial spectrum Prolonged or continuous infusion strongly recommended	Optional when there is a higher likelihood of <i>P. aeruginosa</i> or enterococcal involvement
<b>CVC infection</b> Multiple equivalent treatment options	1st	High dose 3GC plus high dose ciprofloxacin or an aminoglycoside	Spectrum includes <i>P. aeruginosa</i> Potentially better <i>S. aureus</i> PK/PD (compared to regular 3GC dose)	Risk of adverse events TDM and max 2 day treatment for aminoglycoside	
	1st	Piperacillin-tazobactam	Spectrum includes <i>E. faecalis</i> and <i>P. aeruginosa</i>	Prolonged or continuous infusion strongly recommended	

	1 <sup>st</sup>	2GC plus high dose ciprofloxacin or an aminoglycoside	Spectrum includes <i>P. aeruginosa</i> Potentially better <i>S. aureus</i> PK/PD of beta-lactam component (compared to regular 3GC dose)	Potentially less optimal Enterobacterales PK/PD of beta-lactam component (compared to 3GC) Risk of adverse events TDM and max 2 day treatment for aminoglycoside	
	Alternative	Flucloxacillin plus high dose ciprofloxacin or aminoglycoside	Optimal <i>S. aureus</i> therapy	No beta-lactam treatment of gram-negative pathogens Higher risk of adverse events TDM and max 2 day treatment for aminoglycoside	Optional, especially when there is a high likelihood of <i>S. aureus</i> involvement
	Alternative	Vancomycin plus gram-negative antibacterial treatment	Spectrum includes coagulase-negative Staphylococci, Enterococci	Potentially less optimal <i>S. aureus</i> treatment	Optional when there is a high likelihood of enterococcal involvement or when the patient has intravascular prosthetic material at risk of secondary infection with low virulent gram-positive pathogens

1533

1534 **6b. Antibacterial therapy in patients with sepsis and increased risk of involvement of**  
1535 **3GCR-E**

1536

1537 **Evidence summary**

1538

1539 A meta-analysis of 21 observational studies by Vardakas et al. compared all-cause mortality of  
1540 carbapenem treatment versus alternative antibiotics in patients with community-acquired and  
1541 healthcare-associated bacteraemia with ESBL-producing Enterobacterales.<sup>92</sup> Alternative antibiotics  
1542 were beta-lactam/beta-lactamase inhibitors (BL/BLIs), cephalosporins (mainly cefepime, which is  
1543 currently not registered in the Netherlands), fluoroquinolones and aminoglycosides. Five studies were  
1544 prospectively executed, 16 retrospectively. Studies were located in Asia (9 studies), Europe (6 studies)  
1545 or the US (4 studies). In total, 1584 patients were included and overall mortality was 20 percent. The  
1546 meta-analysis showed no difference in all-cause mortality between carbapenems and BL/BLIs for both  
1547 empirical (RR 0.91, 95% CI 0.66–1.25) and definitive (RR 0.52, 95% CI 0.23–1.13) treatment of ESBL-  
1548 positive bacteraemia. Carbapenems were associated with lower mortality than cefepime for empirical  
1549 (RR 0.51, 95% CI 0.32–0.82) and definitive (RR 0.34, 95% CI 0.22–0.52) treatment. Patients treated with  
1550 carbapenems had lower mortality compared to those treated with fluoroquinolones as empirical  
1551 treatment (RR 0.34, 0.19–0.62), but not as definitive treatment (RR 0.63, 95% CI 0.34–1.15). A  
1552 subgroup analysis for aminoglycoside-based treatment was not reported.

1553

1554 Another systematic review compared carbapenems to alternative antibiotics for the treatment of  
1555 bloodstream infections caused by Enterobacterales with intrinsic, chromosomally encoded AmpC  
1556 beta-lactamase (*Enterobacter*, *Serratia*, *Citrobacter*, *Providencia*, *Morganella* spp).<sup>155</sup> Eleven  
1557 observational studies that assessed all-cause mortality of empirical and/or definite therapy were  
1558 included. Alternative antibiotics were BL/BLIs (piperacillin-tazobactam or ticarcillin-clavulanate),  
1559 cefepime and fluoroquinolones. The meta-analysis showed no significant difference in mortality  
1560 between BL/BLIs versus carbapenems for empirical therapy (OR 0.48; 95% CI 0.14–1.60) or definitive  
1561 therapy (OR 0.87, 95% CI 0.32–2.36) and between cefepime versus carbapenems as empirical therapy  
1562 (0.60; 95% CI 0.17–2.20) or as definitive therapy (OR 0.61; 95% CI 0.27–1.38). Patients treated with  
1563 fluoroquinolones as definite treatment had lower odds of dying, probably reflecting the clinical  
1564 stability that allowed for the only oral therapy option.

1565

1566 One randomized open-label trial compared ertapenem to cefepime and piperacillin-tazobactam for  
1567 the treatment of febrile urinary tract infections due to ESBL-producing *E. coli*.<sup>156</sup> Almost one-third of  
1568 patients had septic shock. Clinical success was defined as resolution of fever and symptoms of UTI  
1569 present at entry with no development of new symptoms. Assignment to cefepime was stopped  
1570 prematurely due to high failure rates (67% clinical failure in 6 patients). Piperacillin-tazobactam (n=33)  
1571 and ertapenem (n=33) were equally effective (94% clinical cure). In both groups two patients (6%) had  
1572 died at day 28.

1573

1574 A systematic review of observational studies summarized mortality of empirical treatment with a BL/BI  
1575 versus carbapenems in patients with bacteraemia due to ESBL-producing Enterobacterales.<sup>157</sup> Types  
1576 of BL/BI included in the studies were not reported. Similar to Vardakas et al.,<sup>92</sup> the authors found no  
1577 significant difference in mortality between treatment arms for empirical and definite treatment.

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The MERINO trial was an international, open-label, randomized controlled, non-inferiority trial comparing definitive therapy with piperacillin-tazobactam to meropenem in patients with bloodstream infections caused by ceftriaxone-resistant, piperacillin-tazobactam and meropenem sensitive *E. coli* and *K. pneumoniae*.<sup>158</sup> Bacteraemia originated from the urinary tract in 60% of patients, 86% of isolates was *E. coli* and 44% of infections was community-acquired. In 43% of patients a qSofa score  $\geq 2$  was recorded. Phenotypic ESBL production was found in 86% of isolates, while AmpC genes were found in 10.2% of isolates. The trial was stopped prematurely as it became very unlikely that continuation of the trial would show non-inferiority of piperacillin-tazobactam. In 378 evaluable patients 30-day all-cause mortality was 12.3% in patients treated with piperacillin-tazobactam and 3.7% in patients treated with meropenem (absolute risk difference 8.6%, 1-sided 97.5% CI -  $\infty$  to 14.5, number needed to harm: 12). Results were consistent in the per-protocol analysis, among pre-specified subgroup analyses and in sensitivity analyses. There was no subgroup in which non-inferiority was shown, including in the subgroup with UTI as the source of bacteraemia and the lowest mortality. There were no significant differences between treatment arms on secondary outcomes including time to clinical and microbiologic resolution of infection, clinical success day 4, microbiologic resolution of infection and secondary infection with resistant MO or CDI. However, all showed a trend favouring meropenem. There was no sign of increased risk of developing infections with resistant microorganisms in the meropenem group, although numbers were small. Almost all deaths were not directly related to the primary infection.

A meta-analysis of Chen et al compared the effect of ceftazidime-avibactam or ceftolozane-tazobactam to alternative treatment strategies for complicated intra-abdominal infections (cIAI) or complicated urinary tract infections (cUTI) with ceftazidime-resistant gram-negative bacteria or ESBL-positive Enterobacterales.<sup>159</sup> Nine high quality RCTs assessing several clinical outcomes in patients with cIAI (5), cUTI (3) or both (1) were included. Overall mortality was 1.1%. There was no difference in clinical treatment success between BL/BI treatment and comparator treatment in the overall analysis (OR 1.07, 95%CI 0.80 – 1.44, 2934 patients). A subgroup analysis comparing BL/BI to meropenem showed no difference in clinical treatment success (OR 0.91, 95% CI: 0.65 – 1.26). Another subgroup analysis in patients with cUTI showed higher chance of clinical treatment success of BL/BI in patients treated for cUTI (OR 2.14, 95% CI 1.06 – 4.31. Two trials with levofloxacin and imipenem as alternative treatments). Patients treated with BL/BI had no significantly different mortality rate (OR 1.14, 95%CI 0.90 – 1.44) or rate of adverse events (OR 1.07, 95%CI 0.94 – 1.44) compared to alternative treatments, including for subgroups of patients with cIAI and cUTI. Three RCTs within the meta-analysis reported on ceftolozane-tazobactam efficacy in patients with ESBL-positive Enterobacterales infection at baseline in cIAI (2 RCTs, comparing to meropenem) and cUTI (1 RCT, comparing to levofloxacin). Clinical cure was higher in patients treated with ceftolozane-tazobactam (OR 2.89, 95% CI 1.18 – 7.09, 172 patients), although this significant difference was only based on the trial in cUTI comparing to levofloxacin. Popejoy et al. confirmed this finding separately based on pooled data on ESBL infections in two of the three trials.<sup>160-162</sup>

We found no RCTs on the effect of empirical aminoglycosides-based therapy in patients with sepsis or severe infections with 3GCR-E.

1622 Except for the mentioned RCT in the systematic review of Chen et al.,<sup>159</sup> there are no RCTs on the effect  
 1623 of fluoroquinolones monotherapy in patients with sepsis or severe infections with 3GCR-E. Similarly,  
 1624 no RCTs were found on the effect of definite therapy with trimethoprim/sulfamethoxazole of such  
 1625 severe infections.

1626

1627 **Conclusions**

Conclusion	Quality of evidence
Pooled observational data in patients with bacteraemia due to ESBL-producing Enterobacterales show decreased mortality of empirical and definite treatment with carbapenems compared to cefepime	Very low <sup>92</sup>
Pooled observational data in patients with bacteraemia due to ESBL-producing Enterobacterales showed no additional effect on mortality of empirical and definite treatment with carbapenems compared to BL/BI	Very low <sup>92, 157</sup>
One RCT in patients with bacteraemia with ESBL-producing <i>E. coli</i> and <i>K. pneumoniae</i> showed a large decrease in 30-day all-cause mortality of definite treatment with meropenem compared to piperacillin-tazobactam The same RCT showed no additional effect on adverse events and secondary infections with resistant microorganisms or <i>C. difficile</i>	High <sup>158</sup>  Low <sup>158</sup>
Pooled observational data in patients with bacteraemia due to ESBL-producing Enterobacterales showed decreased mortality of empirical treatment with carbapenems compared to fluoroquinolones and no additional effect of definite treatment with carbapenems compared to fluoroquinolones	Very low <sup>92</sup>
There was insufficient data in patients with sepsis due to 3GCR-E to conclude on the effect of empirical treatment with aminoglycoside-based therapy	-
Pooled observational data in patients with bacteraemia due to chromosomally-encoded AmpC-producing Enterobacterales (such as <i>Enterobacter</i> , <i>Serratia</i> , <i>Citrobacter</i> , <i>Providencia</i> and <i>Morganella</i> species) showed no additional effect on mortality of empirical and definite treatment of carbapenems compared to BL/BI	Very low <sup>163</sup>
Pooled data from RCTs in patients with complicated intra-abdominal and urinary tract infections in general showed no additional effect on clinical cure, mortality and adverse events of newer BL/BI compared to alternative treatments (mainly meropenem)	Low <sup>159</sup>
Pooled data from RCTs in patients with complicated intra-abdominal and urinary tract infections due to ESBL-producing Enterobacterales showed increased clinical cure of ceftolozane-tazobactam compared to alternative treatments (mainly levofloxacin)	Low <sup>159</sup>

1628

1629 **Other considerations**

1630 Providing evidence-based recommendations for empirical treatment of sepsis caused by  
 1631 Enterobacterales resistant to 3<sup>rd</sup> generation cephalosporins (3GCR-E) is complex. There is a lack of RCTs  
 1632 focussing on sepsis due to HRMO only and available studies are heterogeneous and have considerable  
 1633 limitations. Definitions and resistance testing of HRMO often differ between studies, in addition to the  
 1634 already mentioned limitations in chapter 3. Apart from mortality other outcomes are hardly assessed.

1635

1636 Carbapenems are not hydrolysed by ESBL and AmpC enzymes and are therefore generally considered  
1637 an appropriate choice for the treatment of severe infections with gram-negative bacteria producing  
1638 these enzymes. This is reflected by the available observational studies that compare alternative  
1639 treatments to carbapenems in patients with sepsis or bacteraemia due to 3GCR-E.<sup>92, 155, 157</sup> However,  
1640 the increasing use of carbapenems has been associated with increasing rates of carbapenem-  
1641 resistance worldwide and the wish to use carbapenem-sparing treatments for antimicrobial  
1642 stewardship purposes.<sup>164</sup>

1643  
1644 The efficacy of beta-lactam/beta-lactamase inhibitors (BL/BIs) has been of specific interest in clinical  
1645 practice, due to in vitro susceptibility of some 3GCR-E to these agents.<sup>165</sup> Three meta-analyses of  
1646 observational studies showed no suggestion that the older BL/BIs (mostly piperacillin-tazobactam) are  
1647 inferior compared to carbapenems for the treatment of bloodstream infections caused by bacteria  
1648 producing ESBL<sup>92, 157</sup> or with chromosomal AmpC (such as *Enterobacter*, *Serratia*, *Citrobacter*,  
1649 *Providencia* and *Morganella* spp).<sup>155, 166</sup> Also, the large European retrospective INCREMENT study  
1650 compared BL/BI to carbapenem treatment in patients with bloodstream infections with ESBL-  
1651 producing Enterobacterales that had in vitro sensitivity to the BL/BI (according to CLSI).<sup>167</sup> The authors  
1652 found no difference in 14-day clinical cure and 30-day mortality between BL/BI and carbapenem  
1653 treatment in their multivariate analysis. A similar post-hoc analysis of patients with ESBL-producing *E.*  
1654 *coli* bacteraemia from six prospective cohorts showed comparable 30-day mortality after empirical and  
1655 definite therapy with BL/BI (piperacillin-tazobactam or amoxicillin-clavulanic acid) compared to  
1656 carbapenems.<sup>101</sup> A case-control study of patients with bacteraemia due to *Enterobacter*, *Serratia*, or  
1657 *Citrobacter* species also found no differences in mortality and persistence of bacteraemia between  
1658 BL/BI and meropenem or cefepime treatment.<sup>168</sup> Importantly, there were differences in source and  
1659 severity of infection, in vitro susceptibilities and dosing strategies between the observational  
1660 studies.<sup>165, 169</sup> In addition, some individual studies within the meta-analyses suggested increased  
1661 mortality in patients with ESBL bacteraemia and treatment with BL/BI compared to carbapenems.<sup>170-</sup>  
1662 <sup>172</sup>

1663  
1664 Concerns about increased mortality in severe infections with 3GCR-E treated with a BL/BI versus  
1665 carbapenems have now been confirmed for *E. coli* and *K. pneumoniae* by the MERINO trial.<sup>158</sup> Although  
1666 questions remain, the committee found the evidence on the difference in mortality convincing enough  
1667 to currently recommend against the use of BL/BI and specifically piperacillin-tazobactam for the  
1668 treatment of sepsis in patients at risk of or with proven involvement of 3GCR *E. coli* and *K. pneumoniae*.  
1669 This also counts for definite therapy of patients who have recovered clinically. As 86% of isolates  
1670 produced ESBL, it is very likely that the MERINO trial findings are generalizable to other ESBL-producing  
1671 Enterobacterales. Future trials should assess if specific subgroups of patients can be safely treated with  
1672 piperacillin-tazobactam. Suggested subgroups in the literature that could be treated with piperacillin-  
1673 tazobactam are patients with urinary source of infection,<sup>156</sup> less severe infections, those infected with  
1674 isolates with low MICs, Enterobacterales with certain types of ESBL-genes, *E. coli* (versus *Klebsiella*  
1675 *spp*), or isolates that only produce chromosomally-encoded AmpC.<sup>163, 165</sup>

1676  
1677 The MERINO trial did not support the suggestion that piperacillin-tazobactam use is safe in patients  
1678 with 3GCR-E bacteraemia and a urinary tract origin. In the primary analysis, the authors found no  
1679 association of mortality with piperacillin-tazobactam MIC (although numbers per MIC were low) or *E.*  
1680 *coli* vs *K. pneumoniae* infection. However, a post-hoc analysis of trial data included piperacillin-

1681 tazobactam MICs by broth microdilution (BMD) in the analyses.<sup>173</sup> It showed that with BMD 17.8% of  
1682 these bacteria would have been categorized as resistant to piperacillin-tazobactam according to  
1683 EUCAST criteria (breakpoint at MIC 8 mg/L) while 6.4% would be resistant according to the Clinical and  
1684 Laboratory Standards Institute from the US (CLSI, who have set the breakpoint at an MIC of 16 mg/L).  
1685 The microbiological modified intention to treat analysis of the MERINO trial data showed increased  
1686 mortality in patients with isolates with piperacillin-tazobactam BMD MICs > 16 mg/L (adjusted OR 2;  
1687 95% CI 1.3 – 3.4). An important limitation of the MERINO trial is that drugs were administered in  
1688 intermittent dosing intervals. Prolonged infusion of beta-lactams, especially of piperacillin-tazobactam  
1689 could have influenced efficacy (see also chapter 10).

1690  
1691 There are conflicting opinions in the literature whether piperacillin-tazobactam is a treatment option  
1692 for severe infections caused by Enterobacterales with chromosomally-producing AmpC.<sup>163</sup> There are  
1693 concerns that strains become resistant to piperacillin-tazobactam during therapy as is shown in vitro  
1694 and clinically with 3<sup>rd</sup> generation cephalosporins for *Enterobacter* bacteraemia.<sup>174</sup> However,  
1695 piperacillin-tazobactam is only a weak inducer of chromosomal AmpC compared to amoxicillin-  
1696 clavulanic acid and 3<sup>rd</sup> generation cephalosporins. There is only one study suggesting in vitro induction  
1697 of high-level AmpC production and there is no guidance by EUCAST on this topic. Observational studies  
1698 have concluded that piperacillin-tazobactam may be a treatment option in comparison to  
1699 carbapenems, but no randomized trials are available.<sup>155</sup>

1700  
1701 For the newer BL/BI's ceftazidime-avibactam and ceftolozane-tazobactam, the mentioned meta-  
1702 analysis of Chen et al. showed that there might be place for these treatments in intra-abdominal and  
1703 urinary tract infections caused by ESBL-producing Enterobacterales. However, sepsis patients were  
1704 hardly included. In addition, because of the activity of the newer BL/BIs against carbapenemase-  
1705 producing Enterobacterales (CPE), the general opinion of the committee was to reserve these agents  
1706 to the treatment of infections with CPE. Emergence of resistance to these agents has been reported.<sup>175,</sup>  
1707 <sup>176</sup>

1708  
1709 Fluoroquinolones were less effective than carbapenems as empirical therapy in observational studies  
1710 on ESBL-producing Enterobacterales bacteraemia, while equally effective as definitive therapy.<sup>92</sup> This  
1711 difference probably reflects again the importance of in vitro susceptibility of the strain. The previously  
1712 mentioned retrospective, European INCREMENT study on bacteraemia with ESBL-producing  
1713 Enterobacterales also compared outcomes of patients treated with aminoglycosides or  
1714 fluoroquinolones to patients treated with carbapenems.<sup>177</sup> Although numbers were very low, there  
1715 were no differences between treatments with regard to mortality, clinical failure and length of stay. In  
1716 ESBL-producing Enterobacterales, the prevalence of resistance to fluoroquinolones and  
1717 aminoglycosides have been found to be high in some publications.<sup>178</sup> Nethmap data presented in  
1718 chapter 2 showed that in the Netherlands approximately two third and one third of ESBL-producing *E.*  
1719 *coli* isolates in blood culture are fluoroquinolone and aminoglycoside resistant, respectively.

1720  
1721 The previously discussed study of Ong et al. showed that a strategy preferring carbapenem over  
1722 aminoglycosides-based treatment in empirical treatment of 3GCR-E sepsis in the Dutch university ICU  
1723 setting led to an increase of carbapenem use of 9%.<sup>66</sup> A carbapenem-based strategy in 3GCR-E sepsis  
1724 would therefore likely further increase carbapenem use in the Netherlands, which is unwanted from  
1725 an antibiotic stewardship perspective. It should be noted that that an aminoglycoside-based regimen

1726 may be a potentially less effective and more toxic strategy compared to carbapenem treatment in  
 1727 patients with sepsis (chapter 6a). Also, approximately 1/3<sup>rd</sup> of ESBL-E in the Netherlands is resistant to  
 1728 aminoglycosides (chapter 2). In conclusion, depending on the perspective, both strategies have  
 1729 important limitations. In summary and as discussed in chapter 6a, the committee has concerns on  
 1730 aminoglycoside efficacy and safety, but does support the use of short-term (max. two days), empirical  
 1731 therapy including aminoglycosides as a carbapenem-sparing strategy.

1732  
 1733 Only very old reports and one recent observational studies have shown efficacy of definite therapy  
 1734 trimethoprim/sulfamethoxazole in serious gram-negative infections, including due to ESBL and  
 1735 chromosomal AmpC-producing Enterobacterales. No randomized trials are available.

1736  
 1737 Regarding empirical therapy in patients with sepsis the committee settled that in those patients with  
 1738 a high risk of 3GCR-E involvement based on prior infection or colonization (chapter 3, recommendation  
 1739 1), we suggest to treat with a carbapenem. This recommendation especially counts for those patients  
 1740 with previous colonisation with ESBL-producing Enterobacterales that had co-resistance to  
 1741 fluoroquinolones and aminoglycosides (versus other causes of 3GCR). Alternative treatment strategies  
 1742 are listed in **Table 7**. We settled that from an antibiotic stewardship perspective a carbapenem-sparing  
 1743 empirical treatment strategy for sepsis is reasonable in patients at increased risk of 3GCR-E  
 1744 involvement, but no known prior (1 year) infection/colonization with 3GCR-E (chapter 3,  
 1745 recommendation 2) . Potential empirical treatment strategies are listed in **Table 7**.

1746  
 1747 For definite therapy of patients with sepsis due to ESBL-producing Enterobacterales, the committee  
 1748 recommends against the use of piperacillin-tazobactam, based on the current evidence from the  
 1749 MERINO trial. The committee considers a carbapenem or ciprofloxacin as appropriate *definite* therapy  
 1750 in case of proven susceptibility. Although there is lack of evidence, we agreed that  
 1751 trimethoprim/sulfamethoxazole is an appropriate alternative as *definite* therapy in case of proven  
 1752 susceptibility after clinical improvement. After discussion, the committee settled that no  
 1753 recommendation can be given for or against empirical and definite piperacillin-tazobactam therapy in  
 1754 sepsis due to chromosomal AmpC-producing Enterobacterales. For recommendations on antimicrobial  
 1755 de-escalation, see chapter 10.

1756  
 1757 **Recommendations**

Recommendation	Strength	Quality of evidence
24. In patients with sepsis and high risk of involvement of 3GCR-E based on prior (1 year) infection/colonization, we recommend meropenem or imipenem as empirical antibacterial therapy. Alternative strategies are listed in <b>Table 7</b>	Strong	Moderate
25. In patients with sepsis and increased risk of involvement of 3GCR-E but no prior (1 year) infection/colonization, we suggest that a carbapenem-sparing strategy (listed in <b>Table 7</b> ) is acceptable	Weak	Very low
26. We cannot provide a recommendation for or against empirical or definite treatment with piperacillin-tazobactam in patients with sepsis due	-	-

to chromosomal AmpC-producing Enterobacterales (such as <i>Enterobacter</i> , <i>Serratia</i> , <i>Citrobacter</i> , <i>Providencia</i> and <i>Morganella</i> spp)		
27. In patients with sepsis due to ESBL-producing Enterobacterales, we recommend against piperacillin-tazobactam as definite antibacterial therapy regardless of the in vitro susceptibility	Strong	Moderate

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CONCEPT

1759 **Table 7. Alternative empirical treatment strategies in sepsis and increased or high estimated risk of involvement of 3GCR-E**

Estimated risk of involvement of 3GCR-E	Choice	Empirical treatment strategy	Advantages	Disadvantages	Note
<b>Increased risk</b>	1 <sup>st</sup>	2GC/3GC plus an aminoglycoside (plus metronidazole when applicable)	Carbapenem-sparing Fluoroquinolone-sparing	Potentially higher risk of adverse events compared to other choices TDM and max 2 day treatment for aminoglycoside Approximately 1/3 <sup>rd</sup> of ESBL-producing Enterobacterales is resistant to aminoglycosides	Equivalent treatment option when there is no known renal insufficiency
	1 <sup>st</sup>	Meropenem or imipenem	Only beta-lactam component of sepsis therapy Potentially lower toxicity profile, especially in case of renal insufficiency	Very broad-spectrum	Equivalent treatment option
	Alternative	2GC/3GC plus high dose ciprofloxacin (plus metronidazole when applicable)	Carbapenem-sparing Aminoglycoside-sparing	Approximately 2/3 <sup>rd</sup> of ESBL-producing Enterobacterales is ciprofloxacin-resistant Risk of adverse events	Optional when local ciprofloxacin resistance allows its empirical use
<b>High risk</b>	1 <sup>st</sup>	Meropenem or imipenem	Only beta-lactam component of sepsis therapy Potentially lower toxicity profile, especially in case of renal insufficiency	Very broad-spectrum	Preferred treatment option, especially when there was previous resistance to aminoglycosides or ciprofloxacin or risk of toxicity (e.g. known renal insufficiency)
	Alternative	2GC/3GC plus an aminoglycoside (plus metronidazole when applicable)	Carbapenem-sparing, Fluoroquinolone-sparing	Potentially higher risk of adverse events compared to other choices TDM and max 2 day treatment for aminoglycoside Approximately 1/3 <sup>rd</sup> of ESBL-producing Enterobacterales is resistant to aminoglycosides	Optional when local resistance epidemiology allows, when there is no sepsis (yet) and/or when the previously cultured 3GCR-E was susceptible

	Alternative	2GC/3GC plus high dose ciprofloxacin (plus metronidazole when applicable)	Carbapenem-sparing Aminoglycoside-sparing	Nationally, approximately 2/3 <sup>rd</sup> of ESBL-producing Enterobacterales is ciprofloxacin-resistant	Optional when local ciprofloxacin resistance allows its use and/or when previously cultured 3GCR-E was susceptible
	Alternative	Piperacillin-tazobactam	Carbapenem-sparing Fluoroquinolone-sparing Aminoglycoside-sparing	Likely inferior in ESBL-producing 3GCR-E sepsis	Only optional when the previously cultured 3GCR-E did not produce ESBL and was susceptible to piperacillin-tazobactam

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### 6c. Antibacterial therapy in patients with sepsis and increased risk of involvement of *Staphylococcus aureus*

#### Evidence summary

We found no systematic reviews comparing the effect of empirical broad-spectrum beta-lactams or aminoglycoside treatment to empirical beta-lactam treatment specifically aimed at methicillin-susceptible *S. aureus* (penicillinase-resistant penicillins and first generation cephalosporins) in patients with sepsis that later turns out to be due to methicillin-susceptible *S. aureus*.

#### Conclusions

Conclusion	Quality of evidence
There are no RCTs or systematic reviews comparing empirical broad-spectrum beta-lactams to empirical treatment specifically aimed at methicillin-susceptible <i>S. aureus</i> (penicillinase-resistant penicillins and first generation cephalosporins) in patients with sepsis that later turns out to be due to methicillin-susceptible <i>S. aureus</i>	-

#### Other considerations

There is no high quality evidence available to provide guidance on the choice of empirical therapy in patients with sepsis in which *S. aureus* is likely to be involved. In these patients broader spectrum empirical therapy with optimal activity against *S. aureus* is needed while awaiting culture results for definite therapy. Some studies suggest that second or 3rd generation cephalosporins or beta-lactam beta-lactamase inhibitors with or without aminoglycosides as empirical therapy are inferior compared to antistaphylococcal penicillins or cefazolin,<sup>179, 180</sup> while other studies support empirical therapy with some of the other beta-lactams.<sup>181</sup> Also for definite therapy with ceftriaxone for *S. aureus* bacteraemia, only a handful retrospective studies with conflicting results are available.<sup>180, 182-186</sup>

The committee ultimately settled that until more high quality data is available, empirical treatment options in patients with sepsis in which *S. aureus* is likely to be involved include all beta-lactams that show in vitro susceptibility to *S. aureus*. Based on PK/PD principles and in line with EUCAST recommendations, we suggest high dosing of ceftriaxone (two times daily 2 grams in normal renal function) or cefotaxim (three times daily 2 grams in normal renal function) in patients with sepsis and substantial risk of *S. aureus* involvement.<sup>187</sup> Alternative treatment strategies are listed in **Table 8**. The committee settled that the clinician should decide on an individual patient basis which strategy is most appropriate.

For definite therapy of *S. aureus* sepsis, we follow the NVMM guideline on *S. aureus* bacteraemia which recommends flucloxacillin in patients with *S. aureus* bacteraemia with cefazolin as an alternative when flucloxacillin is (relatively) contraindicated.<sup>8</sup>

#### Recommendations

Recommendation	Strength	Quality of evidence
<p>28. There is insufficient evidence to recommend against empirical use of other beta-lactam antibiotics than flucloxacillin or cefazolin in patients with sepsis in which <i>S. aureus</i> is a likely pathogen.</p> <p>Empirical sepsis treatment strategies when there is a substantial risk of <i>S. aureus</i> involvement are listed in <b>Table 8</b></p>	-	-
<p>29. For definite therapy of patients with sepsis due to <i>S. aureus</i>, we refer to the Dutch guideline on <i>S. aureus</i> bacteraemia.<sup>8</sup></p>		

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1798

CONCEPT

1799 **Table 8. Alternative empirical treatment strategies in sepsis and suspected *S. aureus* involvement**

Empirical treatment strategy	Advantages	Disadvantages	Note
3GC high dose	Potentially better <i>S. aureus</i> PK/PD compared to standard dose 3GC	Clinicians may not be used to higher dosing	In accordance with EUCAST recommendation
Flucloxacillin-based therapy	Optimal <i>S. aureus</i> therapy	Combined with ciprofloxacin or aminoglycoside: no beta-lactam treatment for gram-negative pathogens; aminoglycoside: higher risk of adverse events, TDM needed. Combined with additional beta-lactams: potentially high fluid loads	
3GC standard dose	No difference in 3GCR-E dosing compared to regular empirical sepsis therapy	Potentially suboptimal <i>S. aureus</i> PK/PD	Not in accordance with EUCAST
Cefuroxime-based therapy	Potentially better <i>S. aureus</i> PK/PD compared to 3GC standard dose	Potentially less optimal Enterobacterales PK/PD compared to 3GC	
Piperacillin-tazobactam		Broad-spectrum	
Meropenem or imipenem		Very broad-spectrum	Primarily reserved for patients at high risk of 3GCR-E
Vancomycin-based therapy		Potentially inferior treatment of <i>S. aureus</i> (compared to flucloxacillin) TDM needed	Optional when beta-lactams are contra-indicated

1800

### 1801 **III Timing and duration of antibacterial therapy in sepsis**

1802

#### 1803 **Introduction**

1804 In the previous edition of the SWAB sepsis guidelines, it was recommended to start antibacterial  
1805 therapy in adult patient with severe sepsis and septic shock as soon as possible, preferably within the  
1806 first hour of presentation. This recommendation is in line with the recommendations of the SSC  
1807 guidelines, including the recently updated hour-1 sepsis bundle stressing the importance of the first  
1808 golden hour and stating that antibacterial therapy should be started *immediately* for patients  
1809 presenting with sepsis or septic shock.<sup>37, 188</sup> However, the importance of this one hour time frame is  
1810 currently being debated. In fact, the Infectious Diseases Society of America (IDSA) recently stated that  
1811 IDSA didn't support the SSC recommendation on antibiotic timing in sepsis, particularly the formulation  
1812 of this fixed 1 hour time period within which antibiotics should be administered.<sup>123</sup> In chapter 8 we  
1813 summarized the available evidence on the topic.

1814

1815 Duration of antibacterial therapy in patients with sepsis and/or bacteraemia has historically been  
1816 based on expert opinion. In studies determining treatment duration practices for patients with  
1817 bacteraemia, patients were generally treated for 7 to 14 days, but with wide variation.<sup>189-191</sup> Longer  
1818 duration of antibacterial treatment is associated with development of antimicrobial resistance and  
1819 with adverse events, such as bacterial superinfections, *Clostridium difficile* infection and death.<sup>192-197</sup>  
1820 Several studies have critically assessed if shorter duration of antibacterial treatment is as effective and  
1821 safe as longer duration in patients with sepsis. In chapter 9 we summarized evidence on the treatment  
1822 duration of sepsis in general or of unknown origin, **specifically for gram-negative bacteraemia**, and of  
1823 sepsis due to VAP/HAP, intra-abdominal infection and SSTI. In addition, we summarized evidence on  
1824 PCT-guided treatment duration and de-escalation in patients with sepsis.

### 1825 **7. What is the optimal timing of empirical antibacterial therapy in patients with** 1826 **sepsis?**

#### 1827 **Evidence summary**

1828 Sterling et al. performed a systematic review and meta-analysis regarding the impact of timing of  
1829 antibiotic administration on outcome in severe sepsis and septic shock patients.<sup>198</sup> The review included  
1830 11 observational studies. A total of 16.178 patients were evaluable for the effect of antibiotic  
1831 administration within 3 hours after triage at the emergency department (ED). Patients who received  
1832 antibiotics more than 3 hours after ED triage had similar mortality rates compared to patients who  
1833 received antibiotics within 3 hours after ED triage (OR 1.16, 95% CI 0.92 to 1.46). A total of 11.017  
1834 patients were evaluable for the effect of antibiotic administration within 1 hour after recognition of  
1835 severe sepsis/septic shock. Patients who received antibiotics more than 1 hour after severe  
1836 sepsis/shock recognition had similar mortality rates compared to patients who received antibiotics  
1837 within 1 hour of recognition (OR 1.46, 95% CI 0.89 to 2.40), but with heterogeneity between studies.  
1838 A sensitivity analysis including 7074 patients showed no significantly increased mortality for each  
1839 additional hour delay in antibiotic administration from recognition of severe sepsis and septic shock.

1840

1841 After publication of the 2015 meta-analysis, one multicentre, open label, randomized trial was  
1842 published.<sup>51</sup> The previously described PHANTASi trial by Alam et al. assessed the impact of prehospital

1843 antibiotic administration in 2698 patients with sepsis, including severe sepsis (58%) and septic shock  
 1844 (4%). This Dutch multi-centre study compared the effects of early administration of antibiotics in the  
 1845 ambulance with standard of care. The 28-day mortality was similar in the intervention and standard of  
 1846 care group (RR 0.95 CI 0.74 – 1.24), regardless of the severity of sepsis. There were no differences in  
 1847 ICU admissions, length of hospital stay and/or 90 day mortality, but readmission was less likely in the  
 1848 intervention group (7 versus 10%, p<0.001). Reasons for re-admission were left unexplained in the  
 1849 manuscript. Median time to antibiotic administration after ED arrival in the standard of care group  
 1850 showed a non-significant decrease after training of the ED staff (93 minutes (IQR 39-140) before versus  
 1851 70 minutes (IQR 36-128) after training, respectively, p 0.14).

1852  
 1853 Two key observational studies have been published after the 2015 meta-analysis.<sup>199, 200</sup> Seymour et al.  
 1854 retrospectively reviewed the influence of time to treatment of 49.331 patients with sepsis and septic  
 1855 shock.<sup>199</sup> They showed that a more rapid completion of the 3-hour bundle of sepsis care was associated  
 1856 with a lower risk-adjusted in-hospital mortality. Also, longer time to antibiotic initiation was associated  
 1857 with an increased in-hospital mortality risk (OR 1.04 for each hour delay, 95% CI 1.02 – 1.05). However,  
 1858 this effect was only seen in those patients with septic shock who received vasopressors. The other  
 1859 retrospective observational study by Liu et al. in 35.000 sepsis patients showed that the adjusted OR  
 1860 for mortality based on each hour delay between antibiotic administration and ED registration was 1.09  
 1861 (95% CI 1.05 – 1.13).<sup>200</sup> Mortality increased with 0.3% for sepsis (95% CI 0.01 – 0.6), 0.4% for severe  
 1862 sepsis (95% CI 0.1 – 0.8) and 1.8% for septic shock (95% CI 0.8 – 3) for each hour delay.

1863  
 1864 **Conclusions**

Conclusion	Quality of evidence
Pooled data in patients with sepsis showed no additional effect of antibiotic administration within 3 hours of ED triage or within 1 hour of severe sepsis/septic shock recognition on mortality	Very low <sup>198</sup>
One randomized trial in patients with sepsis showed no additional effect of pre-hospital antibiotic administration compared to usual care on 28-day mortality	Low <sup>51</sup>
Two large observational studies in patients with sepsis showed that longer time to antibiotic administration was associated with increased mortality in patients with septic shock.	Low <sup>199, 200</sup>
Two large observational studies in patients with sepsis showed conflicting effects of longer time to antibiotic administration for patients with sepsis and severe sepsis (excluding patients with septic shock)	Very low <sup>199, 200</sup>

1865  
 1866 **Other considerations**

1867 The recommendation on timing of antibiotic therapy in patients with sepsis in the previous SWAB  
 1868 sepsis guideline was mainly based on the results of the landmark study by Kumar et al. in 2006 showing  
 1869 that each hour delay in antibiotic therapy resulted in an average decrease in survival of 7.6%.<sup>25</sup> Since  
 1870 then, other retrospective observational studies underlined Kumar’s findings forming the basis for the  
 1871 recently updated recommendations of the SSC guidelines.<sup>188, 199-201</sup> The one more recent meta-analysis,  
 1872 which included the aforementioned observational studies, however did not show a significant  
 1873 mortality benefit of administering antibiotics within 3 hours of ER triage or within 1 hour of shock  
 1874 recognition in sepsis.<sup>198</sup> In line, the one randomized trial on this topic could not demonstrate an effect

1875 of faster (prehospital) antibiotic administration for sepsis on outcome in a Dutch setting.<sup>51</sup> This study  
1876 however only included only a small number of patients with septic shock.

1877

1878 There are several limitations related to the observational character of most of these studies that are  
1879 important to consider when using the results to formulate recommendations on antibiotic timing in  
1880 sepsis. First of all, time zero is open to multiple interpretations and difficult to define as the exact onset  
1881 of infection is generally unknown. Studies use different definitions of time zero including time of  
1882 presentation to the ED, onset of hypotension or time of initiation of the sepsis bundle. Moreover, the  
1883 question is which endpoints are to be chosen, e.g. time to administration of the first antibiotic, of all  
1884 antibiotics or of antibiotics that are actually active *in vitro*. In any case, the exact time between the  
1885 onset of infection and antibiotic administration is variable, at least to some extent and therefore the  
1886 biological plausibility that each additional hour delay of antibiotic administration has such a huge  
1887 impact on survival could be argued.<sup>202</sup> Second, in most studies the appropriateness of the antibiotic  
1888 regimens is not taken into account. Although there is also considerable heterogeneity in definitions of  
1889 this parameter, information on whether the micro-organism cultured is susceptible to the empirical  
1890 broad spectrum antibiotic regimen chosen, is of importance when interpreting the impact of timing of  
1891 antibiotic administration in sepsis. It is of importance however to note that in a considerable part of  
1892 sepsis patients, no causative pathogen is identified and thus appropriateness of antibiotic regimens  
1893 cannot be assessed. Third, when considering the importance of rapid antibiotic administration, the  
1894 proportion of patients in which antibiotics were unjustified because of the absence of infection should  
1895 be taken into account. In this context, a recent Dutch study showed that only 57% of all patients  
1896 admitted to the ICU for presumed sepsis, were actually considered as having either probable or  
1897 definite infection meaning that a fair proportion of patients did not have an actual infection and  
1898 received unnecessary antibiotics.<sup>32</sup> It is well known that antibiotic use has potential harmful  
1899 consequences such as infection with *Clostridium difficile*, side effects, allergies and the emergence of  
1900 drug resistance. A fourth drawback of observational studies is confounding by indication.<sup>203</sup> On the one  
1901 hand, delay in antibiotic administration in patients with presumed sepsis could imply difficulties in the  
1902 diagnostic process as well as to the choice of empirical antibiotic regimen due to multi-drug resistance  
1903 in a complex patient. On the other hand, more rapid antibiotic administration could also be related to  
1904 disease severity as it is reasonable to assume that critically ill patients receive antibiotics at the earliest  
1905 possible, but perhaps at the cost of appropriateness as not enough time has been spent on reviewing  
1906 the medical and microbiological histories of the patient including valuable information on potential  
1907 drug-resistance and former allergic reactions.

1908

1909 Taken all of this into account, it seems reasonable to state that in the critically ill patients with septic  
1910 shock, there is little margin for error and therefore to administer antibiotics as soon as possible. This  
1911 is supported by the results of Seymour et al. and Liu et al. showing that the impact of antibiotic delay  
1912 was most pronounced in the patients with septic shock.<sup>199, 200</sup> On the other hand, in patients with less  
1913 severe disease, rapid antibiotic administration should be weighed against the negative impact of  
1914 potentially unjustified antibiotic use when the patient turns out not to suffer from sepsis.<sup>123, 202, 203</sup> In  
1915 patients with less-severe disease there is often more time for gathering appropriate diagnostic  
1916 information and – in some cases – even prevent the administration of broad-spectrum antibiotics.

1917

1918 The SWAB sepsis guidelines committee therefore agreed to follow the view point of the IDSA arguing  
1919 against defining a fixed time point within which antibiotics should be administered under all

1920 circumstances in patients with sepsis and septic shock. In line with the results published by Alam et al.  
 1921 on the impact of ED staff training on time to antibiotic administration and with the recent IDSA position  
 1922 statement, the committee encourages the efforts to improve the process of antibiotic administration  
 1923 once the decision is made by the physician to start antibiotic therapy in patients with presumed  
 1924 sepsis.<sup>51, 123</sup>

1925  
 1926 **Recommendations**

Recommendation	Strength	Quality of evidence
30. In patients with sepsis or septic shock, we recommend that the administration of antibacterial treatment should be initiated promptly with health care systems working to reduce that time to as short a duration as feasible	Strong	Low

1927

1928 **8. What is the optimal duration of antibacterial treatment for sepsis?**

1929 **Evidence summary**

1930 Antibacterial treatment duration in patients with sepsis

1931 We found no RCTs on the optimal treatment duration in adults with sepsis of unknown origin, sepsis  
 1932 due to cholangitis or sepsis due to suspected infected CVC. Several studies addressed optimal  
 1933 treatment duration in patients with severe abdominal infections, VAP/HAP as well as patients with  
 1934 gram-negative bacteraemia.

1935  
 1936 In 2015 a trial from the US on the appropriate duration of antibacterial therapy of intra-abdominal  
 1937 infections was published.<sup>204</sup> The study compared a fixed duration of four days of antibiotics to  
 1938 antibiotics until two days after resolution of symptoms with a maximum duration of 10 days in patients  
 1939 with complicated intra-abdominal infection and adequate source control. Mean APACHE II score was  
 1940 10, although this score was not reflected in the overall low study mortality of 1%. There was no  
 1941 difference between patients treated for four days and patients treated until two days after resolution  
 1942 of symptoms (5-10 days) in the composite outcome of surgical-site infection, recurrent intra-  
 1943 abdominal infection and 30-day mortality. There were no differences in the occurrence of adverse  
 1944 events. Findings were consistent in two post-hoc analyses that focused on the subset of patients in  
 1945 this cohort with sepsis and those with a high risk of treatment failure.<sup>205, 206</sup>

1946  
 1947 The DURAPOP trial was a French multicentre, randomized, controlled unblinded study comparing an  
 1948 antibacterial therapy duration of 8 days with 15 days following source control of postoperative intra-  
 1949 abdominal infections (PIAI) in critically ill patients.<sup>207</sup> Of 236 patients included in the analysis, 62% had  
 1950 a SAPS score >40, indicating severe infection, and 16% had secondary bacteraemia. Antibiotic  
 1951 treatment choices, including de-escalation, were decided by the treating physician and in accordance  
 1952 to national guidelines. The primary outcome was the number of antibiotic-free days, which was higher  
 1953 in the shorter duration group than in the longer duration group (15 vs 12 days, respectively; P <  
 1954 0.0001). There was no difference between groups in 45-day mortality or other secondary outcomes at  
 1955 day 45 (ICU stay, hospital stay, emergence of multidrug-resistance (MDR) and reoperation rate). Pre-

1956 specified subgroup analysis suggested that in patients with *Pseudomonas* infection the risk of  
1957 emergence of and treated with longer treatment duration more frequently developed MDR compared  
1958 to those treated with a shorter duration.

1959

1960 Several meta-analysis studied short- versus long-duration of antibiotic regimens for VAP and HAP in  
1961 critically ill adults.<sup>38, 208, 209</sup> One of these was performed by the IDSA HAP/VAP guideline committee  
1962 which included additional information from the conductors of the individual RCTs.<sup>38</sup> The majority of  
1963 studies included patients with sepsis, septic shock or severe illness, but data on sepsis patients were  
1964 not available separately. These meta-analysis showed that a fixed period of 7 to 8 days of antibiotic  
1965 treatment duration did not result in differences in 28-day mortality, clinical cure or incidence of  
1966 recurrent pneumonia when compared to a longer, 10 to 15 day antibiotic treatment duration. For the  
1967 subgroup of patients with VAP due to non-fermenting gram-negative bacilli, the meta-analysis showed  
1968 no difference between treatment duration groups in mortality, clinical cure and recurrences.

1969

1970 Two meta-analysis compared 7-day with 14-day antibiotic treatment in patients hospitalized with  
1971 gram-negative bacteraemia.<sup>210, 211</sup> Lee et al. included four RCTs, resulting in 3729 patients with gram-  
1972 negative bacteraemia.<sup>210</sup> Their primary and only outcome was 90-day all-cause mortality. One included  
1973 study focused only on Enterobacterales bacteria,<sup>212</sup> three studies allowed bacteraemia by all gram-  
1974 negative bacteria.<sup>213-215</sup> The BALANCE trial, a large RCT including patients with bloodstream infections  
1975 across 74 hospitals in 7 countries, contributed 68,3% of the patients included in this systematic review  
1976 and meta-analysis.<sup>214</sup>

1977 Overall, 1817 of the included patients in the meta-analysis were men (48.7%) and 1912 women  
1978 (51.3%). The median age ranged from 67-79 years. Most infections were caused by species in the  
1979 Enterobacterales order (90.8%). The main causative pathogen was *E. coli* (63,3%), followed by  
1980 *Klebsiella* spp (19,6%) and *Enterobacter* spp (7,1%). The main source of bacteraemia was the urinary  
1981 tract (51,7%). Within 90 days, 226 patients (12.0%) receiving 7 days of antibiotics died compared with  
1982 253 (13.7%) receiving 14 days. No significant difference in 90-day all-cause mortality was found  
1983 between the 7-day and 14-day group (RR 0.91, 95% CrI, 0.69-1.22) in the intention to treat analysis,  
1984 with a 97.8% probability of noninferiority. The per protocol analysis showed similar results.

1985 Turjeman et al. performed a similar meta-analysis<sup>211</sup>, including three of the RCTs.<sup>212, 213, 215</sup> Their  
1986 primary outcome was 90-day all-cause mortality. No significant difference in mortality was found  
1987 between 7 and 14 days of treatment (OR 1.08, 95% CI 0.73-1.58). In addition, no significant differences  
1988 were found for secondary outcomes, including relapse of bacteraemia (1.00, 0.50-1.97), length of  
1989 hospital stay (P = 0.78), readmission (0.96, 0.80-1.22) and infection complications (local complications:  
1990 1.62, 0.76-3.47; distant complications: 2.00, 0.18-22.08), and for adverse events or emergence of  
1991 resistance.

1992

1993 Two additional meta-analyses compared 7-day and 14-day antibiotic treatment in hospitalized patients  
1994 with bloodstream infections.<sup>216, 217</sup> 78,2% of the total number of inclusions were patients with a gram-  
1995 negative bacteraemia. Similar results were found for the primary outcome 90-day all-cause mortality,  
1996 and for the secondary outcomes and safety outcomes. All systematic reviews had some concern for  
1997 bias due to deviation from the intended intervention, as is the case for open-label trials, but were  
1998 otherwise considered at low risk of bias. Also, wide confidence intervals were the result of small sample  
1999 sizes, especially for a number of the secondary outcomes.

2000

2001 A recent randomized multicenter, open-label, non-inferiority trial performed by Arns et al., which was  
2002 not included in the above mentioned meta-analyses, compared 7-day with 14-day antimicrobial  
2003 therapy for patients with ICU-acquired severe infections by multidrug-resistant gram-negative  
2004 bacteraemia.<sup>218</sup> The trial was terminated prematurely due to low recruitment rate. A total of 106  
2005 patients were included, less than the planned 520 sample size. Most infections were of the respiratory  
2006 tract (68.9%) and caused by carbapenem-resistant Enterobacterales (39.6%). Clinical failure, defined  
2007 as death or relapse of infection at 28 days, occurred in 42.4% and 44.7% in 7- and 14-day groups,  
2008 respectively (risk difference - 2.3, 95% CI, - 21.3 - 16.7). Non-inferiority could not be determined for  
2009 this patient group due to the low sample size.

2010

2011 For duration of treatment in patients with sepsis due to CAP, UTI, SSSI and CNS infection and of sepsis  
2012 due to *S. aureus* infection, we refer to other guidelines.<sup>4-9</sup>

2013

#### 2014 Procalcitonin (PCT)-guided antibiotic treatment duration

2015 The SWAB guideline on antimicrobial stewardship recommends to consider PCT-guided antibiotic  
2016 treatment discontinuation in the ICU setting.<sup>34</sup> Several RCTs, including a large trial in Dutch ICU's,  
2017 demonstrated that PCT-guided antibiotic treatment can result in shorter antibiotic treatment duration  
2018 without an increase in length of hospital stay or mortality.<sup>41, 219</sup> An individual patient data meta-analysis  
2019 of 4482 critically-ill patients included in 11 trials compared PCT-guided antibiotic treatment to standard  
2020 of care in patients with severe infection.<sup>220</sup> Around 50% of included patients had a pulmonary focus  
2021 and almost 20% an intra-abdominal focus of sepsis. More than 70% of patients met sepsis-3 criteria  
2022 and studies were mostly European. Study protocols were similar and recommended discontinuation  
2023 of antibiotics if PCT decreased below 0.5 mg/L or more than 80% from peak level. Mortality was lower  
2024 in patients in the PCT-guided group compared to controls (21.1% versus 23.7%; adjusted OR 0.89, 95%  
2025 CI 0.80 – 0.99). Sepsis severity or focus did not change the effect on mortality. Patients with PCT-guided  
2026 treatment had a significantly shorter antibiotic treatment duration than controls (adjusted coefficient  
2027 -1.19 days, 95% CI -1.73 to – 0.66). A second regular meta-analysis showed similar findings of PCT-  
2028 based discontinuation of antibiotics in critically ill patients.<sup>221</sup> Another individual patient data meta-  
2029 analysis from 523 patients in 13 trials compared PCT-guided antibiotic treatment to standard of care  
2030 in ICU patients with bacteraemia.<sup>222</sup> In line with the previous meta-analysis, PCT-guided antibiotic  
2031 treatment duration resulted in shorter treatment duration compared to controls (–2.86 days; 95% CI:  
2032 –4.88 to –0.84) with similar mortality rates in both groups (16.6% versus 20.0%). A final meta-analysis  
2033 found similar effects of PCT-guided discontinuation of treatment on mortality in critically ill patients,  
2034 but not in the subgroup of patients with sepsis.<sup>223</sup> Also, this meta-analysis showed that the improved  
2035 mortality of the PCT-based strategy was mainly seen in studies that had lower protocol adherence or  
2036 used algorithms of PCT combined with CRP.

2037

#### 2038 De-escalation

2039 Several meta-analyses have summarized evidence on the effect of antibiotic de-escalation (ADE) in  
2040 patients with sepsis or severe infections.<sup>224-227</sup> The most recent meta-analyses showed decreased  
2041 mortality in patients with ADE compared the control group.<sup>224-226</sup> However, these reports included  
2042 observational studies in their analyses. Also, one meta-analysis clearly showed that patients with  
2043 clinical improvement and other parameters associated with lower risk of treatment failure had a  
2044 significantly higher likelihood of receiving ADE in the included studies, indicative of confounding by  
2045 indication.<sup>225</sup> A subgroup analysis of patients with bacteraemia or severe sepsis found a non-significant

2046 lower mortality rate in the ADE group (adjusted OR 0.71; 95% CI 0.47 – 1.05).<sup>224</sup> On the other hand, a  
 2047 subgroup analysis restricted to the RCTs showed an almost significantly higher mortality rate in the  
 2048 ADE group (OR 1.72; 95% CI 0.97 – 3.07), although there was risk of bias and one RCT was on patients  
 2049 with CAP.<sup>224</sup> A French multicentre, non-blinded trial by Leone et al compared ADE to continuation of  
 2050 empirical therapy among 116 ICU patients with severe sepsis.<sup>228</sup> The study showed that ADE can be  
 2051 associated with longer duration of ICU stay (primary outcome, mean difference 3.4; 95% CI –1.7 to 8.5)  
 2052 as well as an increase in superinfections. ADE did not affect 90-day mortality.

2053  
 2054 We found no studies that focussed on ADE in patients with sepsis in which no causative agent could  
 2055 be identified.

2056  
 2057 **Conclusions**

Conclusion	Quality of evidence
One randomized trial in patients with complicated intra-abdominal infections and adequate source control showed no additional effect of a treatment duration until two days after resolution of symptoms (5-10 days) compared to a fixed four day treatment duration on a composite outcome of surgical-site infection, recurrent intra-abdominal infection and 30-day mortality	Moderate <sup>204-206</sup>
One randomized trial in ICU patients with severe post-operative intra-abdominal infections and adequate source control showed that a treatment duration of 8 days led to more antibiotic-free days compared to a duration of 15 days, with no additional effect on 45-day mortality, length of stay, emergence of MDR and reoperation rate	High to moderate <sup>207</sup>
There are no trials or systematic reviews in patients with sepsis and cholangitis comparing shorter treatment duration to regular or longer treatment duration	-
There are no trials or systematic reviews in patients with sepsis and suspected CVC infection comparing shorter treatment duration to regular or longer treatment duration	-
Pooled RCT data in patients with gram-negative bacteraemia showed no additional effect of 14 days of treatment duration compared to 7 days of treatment duration on 90-day mortality	High <sup>212-215</sup>
Pooled RCT data in patients with gram-negative bacteraemia showed no additional effect of 14 days of treatment duration compared to 7 days of treatment duration on relapse of bacteraemia, length of hospital stay, readmission rate and infection complications	Moderate <sup>212-215</sup>
One randomized trial in patients with ICU-acquired severe infections by multidrug-resistant gram-negative bacteria was not able to determine non-inferiority of 7-day compared to 14 days of treatment due to early termination related to the low recruitment rate.	Low <sup>218</sup>
Pooled data in critically ill patients with sepsis showed lower or similar mortality rates and lower antibiotic treatment duration with procalcitonin-guided antibiotic treatment compared to standard care	Moderate <sup>220-223</sup>

Pooled, adjusted observational data in patients with sepsis showed that antibiotic de-escalation was not associated with higher mortality rates compared to standard care	Very low <sup>224-226</sup>
Pooled RCT data in patients with sepsis showed a non-significant increased mortality rate with antibiotic de-escalation compared to standard care	Low <sup>224</sup>
One RCT in patients with severe sepsis showed an increased length of ICU stay and more superinfections with antibiotic de-escalation compared to continuation of empirical therapy. The data showed no effect on mortality.	Moderate <sup>228</sup>
There are no trials or systematic reviews in patients with sepsis and negative cultures comparing antibiotic de-escalation to continuation of empirical therapy	-

2058

2059 **Other considerations**

2060 Although there is some evidence available on antibacterial treatment duration, aggregation of  
 2061 evidence for sepsis is complicated by heterogeneity on causes of bloodstream infections,  
 2062 comorbidities, variety in choice, route and efficacy of antibiotics, causative micro-organisms and other  
 2063 factors such as source control.<sup>214, 229</sup>

2064

2065 Several meta-analyses,<sup>38, 208, 209</sup> an RCT<sup>213</sup> as well as a large propensity-adjusted observational study<sup>230</sup>  
 2066 consistently showed that shorter duration of treatment is as effective and safe as the traditional,  
 2067 longer duration of treatment, in patient with sepsis. Similar results have been found in patients with  
 2068 mild to moderate-severe CAP,<sup>7</sup> acute cholecystitis excluding sepsis,<sup>231</sup> pyelonephritis,<sup>232</sup> uncomplicated  
 2069 cellulitis,<sup>233</sup> non-perforated appendicitis,<sup>234</sup> and bacteraemia.<sup>235</sup> In line, indirect evidence from the  
 2070 studies on PCT-guided discontinuation of antibacterial treatment in patients with sepsis in the ICU  
 2071 setting also suggests that shorter antibacterial treatment duration is safe without a detrimental effect  
 2072 on mortality.<sup>41, 219, 220, 236</sup> These data, together with the potential adverse effects of antibiotic overuse,  
 2073 strengthen the committee to support the SSC recommendation of shorter durations of antibiotic  
 2074 therapy in most patients with sepsis.

2075

2076 We recommended shorter treatment duration of 1-3 days in patients with sepsis due to cholangitis or  
 2077 cholecystitis following adequate source control.<sup>29</sup> This was supported by a Dutch observational study  
 2078 and has been daily practice in many Dutch hospitals.<sup>60</sup> Although there is lack of high quality evidence,  
 2079 the committee is not aware of high clinical failure rates. We therefore still suggest to treat for 1-3 days  
 2080 following adequate source control in patients with sepsis due to cholangitis. **In 2026, a Dutch  
 2081 randomized multicentre trial (COBRA) will report clinical outcomes of 1 day antibiotic treatment  
 2082 compared to 4 to 7 days treatment in patients with acute cholangitis after adequate endoscopic biliary  
 2083 drainage, including patients with bacteraemia (ClinicalTrials.gov: Identifier NCT05750966).**

2084

2085 We agreed that the evidence supports a duration of 7 days in most patients with sepsis due to VAP,  
 2086 and a duration of 4 days in most patients with sepsis due to intra-abdominal infections who have had  
 2087 adequate source control. There is lack of evidence on optimal antibiotic treatment duration for sepsis  
 2088 due to HAP.<sup>38</sup> In line with the IDSA guideline on HAP and VAP, the SWAB sepsis committee felt that it  
 2089 is reasonable to extrapolate evidence from trials with patients with VAP. We therefore agreed on a  
 2090 weak recommendation for a treatment duration of 7 days for most patients with sepsis due to HAP.

2091

2092 For sepsis due to suspected CVC infection there is no high quality evidence available on treatment  
2093 duration. The committee extrapolated from the RCT of Yahav et al. that for most patients with sepsis  
2094 due to CVC infection with Enterobacterales and following removal of the CVC and with favourable  
2095 clinical response a treatment duration of maximum 7 days is likely sufficient. This was supported by  
2096 recent evidence.<sup>214</sup> For enterococci and CNS there is no available evidence but as discussed in chapter  
2097 6a, empirical treatment is often withheld and removal of the CVC might be sufficient. The committee  
2098 therefore settled to suggest 0 to 7 days for sepsis due to suspected CVC infection with CNS or  
2099 enterococci.

2100  
2101 The previous SWAB sepsis guideline suggested that an antibacterial treatment duration of 7 days is  
2102 adequate for most patients with gram-negative bacteraemia, based on limited evidence. Recent high-  
2103 quality evidence supports a 7-day antibiotic treatment duration for most patients with gram-negative  
2104 bacteraemia, including sepsis. Studies do not focus on sepsis specifically, but 55% of patients included  
2105 in the BALANCE trial were admitted in the ICU at enrollment, accounting for one-third of the total  
2106 patient population. Subgroup analyses stratified according to admission in the ICU and APACHE II  
2107 scores showed no different results with respect to death by 90 days for these subgroups.  
2108 The majority of gram-negative infections was caused by Enterobacterales (90.8%). Evidence for other  
2109 gram negative pathogens, such as nonfermenters, is still limited. An ongoing trial in bloodstream  
2110 infections due to *P.aeruginosa* (SHORTEN-2 trial) will provide important complementary evidence  
2111 outside the dominant pathogens (ClinicalTrials.gov: Identifier NCT05210439).

2112  
2113 For sepsis in general or of (yet) unknown focus, we agreed that for most patients with a favourable  
2114 clinical response, a treatment duration of 7 days will be sufficient - or can even be shortened - although  
2115 there is only indirect evidence to support this statement.<sup>213, 214</sup> The committee also agreed that the  
2116 available evidence indirectly supports that source control is a fundamental component of sepsis  
2117 treatment, as discussed below.

2118  
2119 Longer treatment durations are generally indicated in patients with insufficient source control  
2120 (abscesses that cannot be drained), and in patients with specific infections, e.g., suspected  
2121 endovascular infection (prosthetic heart valves or endovascular grafts), bone-and joint infection, men  
2122 with urinary tract infections and potential involvement of the prostate and SSSI.<sup>4, 5, 237</sup> Longer,  
2123 individualized courses may also be considered in patients who are severely immunocompromised and  
2124 patients with sepsis who have a slow clinical response. Of note however, slow clinical response should  
2125 also lead to additional work-up of a new or persistent focus of infection rather than to unsubstantiated  
2126 prolongation of antibiotics. Longer treatment duration is recommended in some infections due to  
2127 specific micro-organisms, such as in *S. aureus* CAP or bacteraemia.<sup>7-9</sup> Other infections outside the scope  
2128 of this guideline that generally need longer antibiotic treatment are bone/joint infections,  
2129 mediastinitis, pleural empyema and endovascular infections.

2130  
2131 The SWAB guideline on antimicrobial stewardship recommends to consider PCT-guided antibiotic  
2132 treatment discontinuation in the ICU setting.<sup>41</sup> More recent studies provide further support for the use  
2133 of PCT-guided treatment duration in critically-ill patients with sepsis as it decreases antibiotic  
2134 treatment duration with improved or similar survival compared to standard care.<sup>220-223</sup> A cost-  
2135 effectiveness analysis suggested that the additional costs of this strategy during hospitalization are  
2136 minimal (i.e. €65), although the cost-effectiveness on the long-term was unclear.<sup>238, 239</sup> Questions

2137 remain however on the usefulness of a PCT-guided antibiotic management strategy in non-ICU sepsis  
2138 patients as well as patients in which a short course of antibiotics is already indicated, such as those  
2139 with sepsis due to an intra-abdominal infection. Also, with increasing antibiotic stewardship efforts  
2140 one could wonder if the positive effects of a PCT-guided antibiotic management strategy on total  
2141 antibiotic consumption will wane over time. And finally, PCT-testing will not be available in all hospitals  
2142 in the Netherlands. In line with the SWAB guideline on antimicrobial stewardship,<sup>41</sup> we therefore gave  
2143 a weak recommendation to use PCT levels to support shortening the duration of antibacterial therapy  
2144 in patients with sepsis if the optimal duration of antibiotic therapy is unclear.

2145  
2146 There are conflicting findings on the efficacy and safety of antibiotic de-escalation (ADE). Overall, there  
2147 is lack of high quality evidence on clinical outcomes of ADE. It is unknown if ADE is an acceptable  
2148 strategy in patients with sepsis in which no causative pathogen can be identified. Similarly, the effect  
2149 of ADE on the development of antibiotic resistance is only assessed retrospectively.<sup>240</sup> Definitions of  
2150 ADE differed among studies, further complicating the interpretation.<sup>225</sup> Here we focused on ADE as a  
2151 strategy to change from broad to a smaller spectrum antibiotics, either by changing or stopping (one  
2152 of) the antibiotics.

2153  
2154 The committee agreed with the SSC good practice statements recommending daily assessment for ADE  
2155 in patients with sepsis based on the potential harm associated with prolonged, unnecessary  
2156 antibiotics.<sup>37</sup> The SWAB antimicrobial stewardship guideline provided a strong recommendation to de-  
2157 escalate antibiotic therapy as soon as culture results become available based on very low quality  
2158 evidence.<sup>41</sup> It should be noted that this guideline did not focus on patients with sepsis. An European  
2159 Society of Intensive Care Medicine (ESICM) and European Society of Clinical Microbiology and  
2160 Infectious Diseases (ESCMID) consensus statement recommends to perform ADE in critically ill patients  
2161 within 24 hours of definite culture results and in vitro susceptibility based on low quality evidence.<sup>241</sup>

2162  
2163 Within the SWAB sepsis guideline committee there was consensus that ADE is appropriate in many  
2164 clinical situations. Taken together, and in line with other relevant guidelines,<sup>37,2941</sup> the committee  
2165 recommends to consider ADE in all patients who are on sepsis treatment, especially when culture  
2166 results become available, in patients beyond 48 hours of treatment and in patients treated with  
2167 antibiotics with high risk of adverse events of the empirical therapy, such as aminoglycosides. We also  
2168 suggest this would include patients in whom only limited or indirect cultures show no causative  
2169 pathogen. In contrast, with current conflicting evidence, including the negative outcomes of ADE in  
2170 one trial on ICU length of stay,<sup>228</sup> the committee felt it is defensible not to perform ADE in individual  
2171 patients. Example situations include a remaining duration of therapy of only one or a few days or the  
2172 impossibility to switch from iv to oral antibiotic treatment.

2173  
2174 Based on evidence summarized in chapters 5, 6a and 6b on aminoglycoside toxicity, the committee  
2175 agreed that duration of empirical aminoglycoside therapy for sepsis should normally not exceed two  
2176 days. We therefore recommend ADE in patients on empirical aminoglycoside therapy preferably within  
2177 a maximum of two days.

2178  
2179 It should be noted that we did not perform an additional evidence summary on iv/oral switch in  
2180 patients with sepsis as this was done in the SWAB antimicrobial stewardship guideline.<sup>41</sup> Only very low  
2181 quality data was available and we were not aware of newer trials or meta-analyses that would change

2182 the conclusions and level of evidence of the antimicrobial stewardship guideline. The SWAB sepsis  
 2183 guideline committee decided to support the recommendation of the SWAB antimicrobial stewardship  
 2184 guideline to switch systemic antibiotic therapy from intravenous to oral antibiotic therapy after 48 -72  
 2185 hours on the basis of the clinical condition and when oral treatment is adequate.

2186  
 2187 Also in line with the SWAB antimicrobial stewardship guideline, we recommend that empirical  
 2188 antibacterial therapy should be discontinued in patients who initially appeared to have sepsis, but  
 2189 subsequently have limited clinical and microbiological evidence of infection.<sup>41</sup> We underscore that for  
 2190 early diagnosis and fast de-escalation options appropriate cultures before start of the antibacterial  
 2191 treatment are crucial. In addition the committee believes that a high turn-around time of tests in the  
 2192 microbiology laboratory, timely reporting of susceptibility results and linkage of test results to  
 2193 antimicrobial stewardship interventions should be improved where possible in order to maximize  
 2194 efforts to give the most appropriate antibiotic treatment for patients with sepsis as soon as possible.<sup>150</sup>

2195  
 2196

**Recommendations**

Recommendation	Strength	Quality of evidence
31. For treatment duration of sepsis due to CAP, UTI, SSSI and of sepsis due to <i>S. aureus</i> infection, we refer to other guidelines <sup>4-9</sup>		
32. We recommend source control interventions when possible to support antibacterial treatment in patients with sepsis.	Strong	Low
33. We recommend that a four-day course of antibacterial treatment is appropriate for patients with sepsis due to intra-abdominal infections following effective source control and with favourable clinical response	Strong	Moderate
34. We suggest that shorter courses of antibacterial treatment (up to three days) are appropriate in patients with sepsis and cholangitis following adequate drainage of the biliary tree	Weak	Very low
35. We recommend that an antibacterial treatment duration of 7 days is adequate for most patients with sepsis due to VAP	Strong	Moderate
36. We suggest that an antibacterial treatment duration of 7 days is adequate for most patients with sepsis due to HAP	Weak	Very low
37. We suggest that an antibacterial treatment duration of 7 days at maximum is adequate for most patients with sepsis due to suspected CVC infection with gram-negative pathogens following removal of the CVC and with favourable clinical response	Weak	Very low
38. We suggest that an antibacterial treatment duration of 0 to 7 days is adequate for most patients with sepsis due to suspected CVC infection with CNS or enterococci following removal of the CVC and with favourable clinical response	Weak	GPS
39. We recommend that an antibacterial treatment duration of 7 days is adequate for most patients with Enterobacterales bacteraemia, including	Strong	Moderate-high

sepsis, unless the underlying diagnosis or lack of source control requires a longer or shorter duration		
40. We suggest that an antibacterial treatment duration of 7 days is adequate for sepsis and septic shock without a clear focus in most patients with favourable clinical response	Weak	Low
41. We recommend daily assessment for the need of antibacterial therapy in patients with sepsis and to discontinue therapy when during follow-up there is lack of clinical or microbiological evidence of infection	Strong	GPS
42. We suggest that procalcitonin levels are used to support shortening the duration of antibacterial therapy in patients with sepsis if optimal duration of antibiotic therapy is unclear	Weak	Moderate
43. We recommend to consider antibiotic de-escalation (resulting in smaller spectrum antibiotics) in all patients on antibiotics for sepsis on a daily basis and based on pathogen identification, sensitivities and risk of adverse events	Strong	Very low
44. We recommend to stop empirical aminoglycoside therapy within a maximum of two days	Strong	Low
45. We recommend to switch systemic antibiotic therapy from intravenous to oral antibiotic therapy after 48 -72 hours on the basis of the clinical condition and when oral treatment is feasible	Strong	Very low

2197

2198

**Table 9. Suggested antibacterial therapy duration in patients with sepsis**

Focus of sepsis	Suggested antibacterial treatment duration
Intra-abdominal infections, following effective source control and with favourable clinical response	Four days <sup>204-207</sup>
Cholangitis, following adequate drainage of the biliary tree	Up to three days <sup>60</sup>
VAP	Seven days <sup>38</sup>
HAP	Seven days
CVC infection with gram-negative pathogen, following removal of the CVC and with favourable clinical response	Up to seven days <sup>213, 214</sup>
CVC infection with CNS or enterococci, following removal of the CVC and with favourable clinical response	Zero to seven days
No clear focus	Seven days <sup>213, 214</sup>

2199

2200 **9. In patients with sepsis, should we recommend pharmacokinetic /**  
 2201 **pharmacodynamic dosing optimization for empirical antibacterial therapy?**

2202 **Introduction**

2203 Pharmacokinetics (PK) describe the time course of drug concentration in body fluids after  
2204 administration of a drug. This time course of drug concentration is dependent on the absorption,  
2205 distribution and elimination of the drug. Pharmacodynamics (PD) describe the relationship between  
2206 drug concentration in body fluids and its pharmacologic effect, i.e. antibacterial effects in the case of  
2207 antibacterial drugs. In vitro and in vivo studies indicate that certain antibacterial drug exposures over  
2208 time (i.e. PK) in relation to antibacterial effects of the drug (i.e. PD) are associated with clinical efficacy  
2209 of the drug.<sup>242-244</sup> These so-called PK/PD indices can differ among antibiotic classes. For beta-lactams,  
2210 clinical efficacy correlates with the percentage of time that the concentration of non-protein bound or  
2211 free fraction (%fT) of the drug in serum is higher than the minimally inhibitory concentration (MIC) of  
2212 the micro-organism (PK/PD index: %fT>MIC).<sup>245</sup> Aminoglycosides have traditionally been considered as  
2213 concentration-dependent antibiotics with C<sub>max</sub>/MIC as the PK/PD index related to clinical efficacy.<sup>246</sup>  
2214 However, several reports suggest that aminoglycoside efficacy is related to both time and  
2215 concentration.<sup>247-250</sup> The PK/PD index that best describes this relation is the ratio of the area under the  
2216 concentration-time curve (AUC) and the MIC, i.e. AUC/MIC ratio. The PK/PD index in most other  
2217 antibiotics is also described by AUC/MIC ratio.<sup>248</sup>

2218  
2219 As discussed in earlier chapters, appropriate antibacterial treatment is associated with improved  
2220 survival of sepsis. However, many pathophysiological changes typical for sepsis patients can alter  
2221 pharmacokinetic properties of antibiotics and can lead to inadequate antibiotic concentrations when  
2222 using standard antibiotic dosing schedules.<sup>248, 251-255</sup> These pathophysiologic changes include kidney  
2223 dysfunction, augmented renal clearing (that is the enhanced renal function sometimes seen in critically  
2224 ill patients), hypoalbuminemia and increased third space due to fluid therapy.<sup>37, 248</sup> Drug  
2225 concentrations of hydrophilic antibacterial agents (such as beta-lactams, aminoglycosides and  
2226 vancomycin) are generally more sensitive to pharmacokinetic changes in patients with sepsis than  
2227 lipophilic antibacterial agents (such as fluoroquinolones). In addition, patients with sepsis may  
2228 generally be at higher risk to be infected with bacteria with higher MICs in comparison to other  
2229 patients.<sup>248</sup>

2230  
2231 For beta-lactams, increasing %fT>MIC can be achieved by increasing beta-lactam total dose, by  
2232 increasing the number of daily doses or by providing extended or continuous infusion. For  
2233 aminoglycosides, C<sub>max</sub>/MIC can be adjusted by the height of the dose. For vancomycin, optimal  
2234 fAUC/MIC could be reached with a loading dose and continuous infusion. The concentrations of  
2235 ciprofloxacin, as a lipophilic agent, are less influenced by PK changes in sepsis, but improved target  
2236 attainment for bacteria with higher MICs could be achieved by increasing the dosing frequency.  
2237 Obesity potentially alters PK-parameters as well.<sup>256, 257</sup> Especially hydrophilic antibacterial agents,  
2238 including beta-lactams and vancomycin, may alter pharmacokinetics in critically ill, obese patients.<sup>258</sup>

2239  
2240 In this chapter we summarized evidence on clinical effects of pharmacokinetic/pharmacodynamic  
2241 dosing optimization of empirical antibacterial therapy in patients with sepsis on the following  
2242 questions:

- 2243 • In patients with sepsis, should antibiotic dosing be based on PK/PD principles?
- 2244 • Is extended or continuous infusion of B-lactam antibiotics superior to intermittent therapy in  
2245 patients with sepsis?
- 2246 • What is the optimal empirical dose of aminoglycosides in patients with sepsis?

- 2247 • Is continuous infusion of glycopeptide antibiotics superior to intermittent therapy in patients  
2248 with sepsis?  
2249 • What is the optimal empirical dose of ciprofloxacin in patients with sepsis?  
2250 • Should we optimize doses in patients with obesity and sepsis?  
2251

### 2252 **PK/PD-based dosing**

2253 Falagas et al. performed a systematic review on the relation between MIC and outcome of infections  
2254 with susceptible gram-negative bacteria.<sup>259</sup> Of the 13 observational studies included, 4 studies  
2255 reported on patients with bacteraemia only (all on beta-lactams) and 5 studies included patients with  
2256 nosocomial infections including bacteraemia (three on beta-lactams, two on tigecycline). Patients  
2257 infected with Enterobacterales with high MICs had higher all-cause mortality than patients infected  
2258 with strains with lower MICs (RR 2.03; 95% CI: 1.05 – 3.92). There was no effect of MIC values on  
2259 treatment failures (RR 1.18; 95% CI: 0.71 – 1.97). Among patients infected with non-fermentative  
2260 gram-negative bacteria, higher MICs were associated with higher all-cause mortality (RR, 2.39; 95% CI,  
2261 1.19 – 4.81) and clinical failure (RR, 5.54; 95% CI, 2.72 to 11.27).  
2262

2263 Jacob et al. performed a meta-analysis on vancomycin MIC and clinical outcomes in patients with MRSA  
2264 infections. A subgroup analysis showed increased risk of clinical failure (RR 1.37; 95% CI: 1.09 – 1.73)  
2265 and mortality (RR 1.46; 95% CI: 1.06 – 2.01) for MIC  $\geq$ 1 mg/L compared to lower MICs in patients with  
2266 MRSA bacteraemia.<sup>260</sup>  
2267

2268 The IDSA guideline on HAP/VAP performed a systematic review of the value of PK/PD-optimized dosing  
2269 on clinical outcomes, with a focus on patients with HAP and VAP.<sup>38</sup> PK/PD-optimized dosing decreased  
2270 mortality (12% vs 24%; RR, 0.49; 95% CI, 0.34 - 0.72) and ICU length of stay (mean difference, -2.48  
2271 days; 95% CI, -3.09 to -1.87 days). PK/PD-optimized dosing showed a benefit on clinical cure (81% vs  
2272 64%; RR, 1.40; 95% CI, 1.16–1.69).  
2273

### 2274 **Use of prolonged infusion of beta-lactam antibiotics over intermittent infusion**

2275 Over the past two decades, numerous RCT have addressed the question whether prolonged beta-  
2276 lactam infusions (either extended or continuous infusion) lead to better clinical outcomes when  
2277 compared to intermittent infusion, which have been the basis for the previous SWAB sepsis guidelines  
2278 (2020) and the IDSA Surviving Sepsis Campaign guideline (2021) recommendations on this subject.<sup>261,</sup>

2279 <sup>262</sup> We now performed a search for the period that was not included in these guidelines (2020-June  
2280 2025), as described in the supplement.  
2281

2282 For the update of this guideline, we identified a recent systematic review and meta-analysis of 18 RCTs  
2283 including the large BLING III and MERCY trials and one new RCT that we used for the current  
2284 recommendations.<sup>263, 264</sup> Since the systematic review used the GRADE system to rate the certainty of  
2285 evidence, we used this assessment and we did not create a new evidence table.  
2286

### 2287 **Summary of evidence**

2288 Abdul-Aziz et al. performed a systematic review and meta-analysis to determine whether prolonged  
2289 beta-lactam antibiotic infusions are associated with a reduced risk of death in critically ill adults with  
2290 sepsis or septic shock compared with intermittent infusions.<sup>263</sup> Prolonged infusion was defined as  
2291 either an extended infusion (intravenous beta-lactam antibiotic administration for 2 hours or longer

2292 during a dosing interval) or a continuous infusion (constant beta-lactam antibiotic administration that  
2293 could be administered as a sequential 6-, 8-, 12-, or 24-hour infusion). Intermittent infusion was  
2294 defined as intravenous beta-lactam antibiotic administration for fewer than 2 hours during a dosing  
2295 interval. Their primary outcome was all-cause 90-day mortality. Secondary outcomes were: ICU  
2296 mortality, ICU length of stay, clinical cure, microbiologic cure and adverse events. A total of 18  
2297 randomized controlled trials were included, resulting in 9108 critically ill adult participants with sepsis  
2298 or septic shock. The BLING III trial contributed 77% of patients included in this meta-analysis.<sup>265</sup>  
2299 Meropenem was studied in 11 trials<sup>265-275</sup>, piperacillin-tazobactam in 8 trials<sup>265, 267, 270, 272, 275-278</sup>,  
2300 cefepime in 3 trials<sup>272, 279, 280</sup>, ticarcillin-clavulanate in 2 trials<sup>270, 275</sup>, and amoxicillin-clavulanate,  
2301 ampicillin-sulbactam, ceftriaxone, and imipenem-cilastatin in 1 trial each<sup>267, 281, 282</sup>. The pooled  
2302 estimated RR for all-cause 90-day mortality was 0.86 (95%-CI 0.72-0.98) for prolonged beta-lactam  
2303 antibiotic infusions compared with intermittent infusions. The number needed to treat for prolonged  
2304 beta-lactam antibiotic infusions to prevent 1 death was 26 patients. This is comparable with the results  
2305 of the BLING III trial, which showed a similar effect estimate but without statistical significance.<sup>265</sup>  
2306 Subgroup analyses showed no difference for meropenem vs piperacillin-tazobactam, culture-positive  
2307 vs culture-negative, gram-negative vs gram-positive infection, kidney replacement therapy vs no  
2308 kidney replacement therapy, lung infection vs other infections, sepsis vs septic shock and male vs  
2309 female patients. Use of prolonged infusion of beta-lactam antibiotic was moreover associated with a  
2310 reduced risk of ICU mortality and increase in clinical cure, whereas there was no difference in terms of  
2311 microbiological cure, adverse events or duration of ICU length of stay. Only one pilot study included in  
2312 this systematic review investigated clinical response for continuous versus intermittent infusion of  
2313 ceftriaxone, an antibiotic frequently used to treat sepsis in the Netherlands.<sup>282</sup> This study randomized  
2314 57 critically ill patients with sepsis on the intensive care unit in the Netherlands to either once-daily  
2315 bolus or continuous infusion of ceftriaxone. No overall statistically significant differences were found  
2316 in clinical outcomes between groups. However, among patients treated for  $\geq 4$  days, continuous  
2317 infusion was associated with better clinical outcomes.

2318  
2319 We found one additional study that was not included in the systematic review. Khan et al. performed  
2320 a randomized trial in a South African ICU comparing 24-hour continuous infusion versus intermittent  
2321 bolus of beta-lactam antibiotics in 122 adults with sepsis.<sup>264</sup> Clinical cure by day 14 was achieved in  
2322 81% of continuous infusion patients and 74.1% of intermittent bolus patients ( $p=0.345$ ), with no  
2323 significant differences in ICU length of stay or antibiotic duration. Mortality at day 90 was lower in the  
2324 continuous infusion group (RR 0.57, 95% CI 0.32–1.01), but this did not reach statistical significance.

2325

### 2326 **Optimal dose of aminoglycosides**

2327 There were no systematic reviews comparing doses of aminoglycosides in patients with sepsis. One  
2328 RCT compared 25 mg/kg to 15 mg/kg amikacin in patients with severe sepsis or septic shock presenting  
2329 in the emergency department.<sup>283</sup> There was no difference in incidence of nephrotoxicity. The number  
2330 of events was, however, very low.

2331

2332 Several systematic reviews of randomized trials showed that once daily dosing is associated with lower  
2333 nephrotoxicity rates compared to multiple dosing, with similar or slightly improved clinical efficacy.<sup>284-</sup>

2334 <sup>287</sup>

2335

### 2336 **Vancomycin continuous dosing**

2337 A systematic review and meta-analysis of two RCTs and nine observational studies summarized  
 2338 evidence on continuous versus intermittent infusion of vancomycin.<sup>288</sup> Eight studies were in the ICU  
 2339 setting and 6 studies included patients with MRSA infections. Five studies reported SAPS II scores  
 2340 (range: 13 – 50).<sup>289</sup> Seven studies reported vancomycin doses (including loading doses) and the authors  
 2341 showed no difference in all-cause mortality of continuous versus intermittent infusion (RR 1.15, 95%  
 2342 CI 0.85 – 1.54); nor in treatment failure (no meta-analysis done) between treatment groups. There was  
 2343 a lower incidence of nephrotoxicity in patients treated with continuous infusion compared to those  
 2344 treated with intermittent infusion of vancomycin (RR 0.61, 95% CI 0.47 – 0.80).

2345

2346 **Optimal dose of ciprofloxacin**

2347 There were no systematic reviews or randomized controlled trials comparing doses of ciprofloxacin in  
 2348 patients with sepsis. We did not systematically summarize PK/PD dosing optimization for other  
 2349 fluoroquinolones.

2350

2351 **Obesity**

2352 There were no systematic reviews nor randomized studies comparing the effect of PK/PD based dosing  
 2353 to standard dosing of antibacterial agents in obese patients with sepsis. Only PK-parameters were  
 2354 evaluated in critically ill obese patients.

2355

2356 **Conclusions**

Conclusion	Quality of evidence
Pooled data in patients with severe infections showed that higher MICs were associated with increased mortality	Low <sup>259, 260</sup>
Pooled data in patients with sepsis due to HAP and VAP showed that PK/PD based dosing (using TDM or extended infusion) was associated with decreased mortality, increased clinical cure and decreased ICU length of stay compared to dosing based on manufacturer's information	Very low <sup>38</sup>
Prolonged beta-lactam antibiotic infusion (extended or continuous) is associated with a reduction in 90-day all-cause mortality and ICU mortality compared with intermittent infusions in critically ill patients with sepsis or septic shock. The benefit of prolonged infusion of beta-lactam antibiotic therapy did not differ across antibiotic type, infection site, pathogen type, presence of renal replacement therapy, or patient sex. Most research focused on carbapenems and piperacillin-tazobactam.	High <sup>263</sup>
One small RCT in patients with sepsis showed that continuous infusion of ceftriaxone was not associated with improved clinical cure	Very low <sup>282</sup>
One RCT in patients with sepsis and septic shock showed that amikacin 25 mg/kg was not associated with increased risk of nephrotoxicity compared to 15 mg/kg	Low <sup>283</sup>
Pooled observational data in critically ill patients showed lower nephrotoxicity and similar mortality rates in continuous vancomycin infusion compared to intermittent infusion of vancomycin	Very low <sup>288</sup>
We found no RCTs or systematic reviews in patients with sepsis comparing the effect of PK/PD-based ciprofloxacin dosing with standard dosing on clinical outcomes	-

We found no RCTs or systematic reviews in obese patients with sepsis comparing the effect of PK/PD-based dosing with standard dosing on clinical outcomes	-
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2357

2358 **Other considerations**

2359 As mentioned before summarizing evidence of antibacterial treatment in sepsis is challenging.  
 2360 Additional challenges in summarizing evidence on PK/PD-based dosing in sepsis are potential  
 2361 differences in PK/PD targets between antibiotics of the same class (for example, higher %T>MIC  
 2362 needed for cephalosporins compared to meropenem),<sup>248</sup> differences in pharmacokinetic dosing  
 2363 interventions (for example, extended or continuous beta-lactam infusion), different pharmacokinetic  
 2364 characteristics between patients and within individual patients over time (for example, due to age,  
 2365 obesity, changes in volume of distribution of the drug, changes in renal function), different or unknown  
 2366 MICs of the causal bacteria and differences in reliability of MIC testing.

2367

2368 The committee agreed with the SSC guideline recommendation to adjust dosing based on PK/PD  
 2369 principles and drug properties in patients with sepsis and septic shock.<sup>37</sup> Evidence supports  
 2370 pharmacokinetically optimized dosing strategies in patients with sepsis and septic shock, but this  
 2371 approach is currently difficult to achieve due to lack of rapid therapeutic drug monitoring options  
 2372 (TDM) for many antibacterial drugs. The high-quality evidence of the effect of prolonged infusion in  
 2373 beta-lactams supports PK/PD-based dosing, but there is low quality or lack of evidence of the effect of  
 2374 PK/PD-based dosing in general, and specifically of aminoglycosides, vancomycin and ciprofloxacin and  
 2375 in obese patients on clinical outcomes. We felt that the available evidence as well as the many studies  
 2376 reporting that PK/PD targets are not reached in sepsis or critically ill patients in general supports a  
 2377 recommendation of PK/PD-based dosing.<sup>37, 248, 290-292</sup> Since EUCAST recommendations on breakpoints  
 2378 are generally accepted and based on PK/PD principles, we generally followed the EUCAST dosing  
 2379 recommendations on doses in specific pathogens.<sup>44</sup>

2380

2381 TDM is not yet available in the Netherlands on a large scale for antibacterial drugs other than  
 2382 aminoglycosides and vancomycin, including for beta-lactams. Due to lack of TDM possibilities for many  
 2383 antibacterial drugs in the Netherlands, we cannot currently give a strong recommendation on TDM for  
 2384 antibacterial therapy except for aminoglycosides and vancomycin. However, we do suggest to consider  
 2385 TDM in patients with sepsis and septic shock when there are concerns on target attainment of other  
 2386 antibacterial drugs than aminoglycoside and vancomycin and when TDM is possible.

2387

2388 Based on the evidence of clinical outcomes of prolonged infusion of beta-lactams in patients with  
 2389 sepsis, the committee agreed to recommend this strategy for carbapenems and piperacillin-  
 2390 tazobactam and to suggest it for other beta-lactams, taking their pharmacokinetic properties into  
 2391 account. Prolonged infusion is feasible when adequate IV access and resources (e.g. availability of  
 2392 infusion pumps) are available. Administration of an appropriate loading dose prior to initiating  
 2393 prolonged infusion is essential to rapidly achieve therapeutic beta-lactam concentrations. In addition,  
 2394 drug stability and compatibility with concomitant intravenous medications should be carefully  
 2395 considered to preserve the effectiveness of antibiotic treatment. For example, some beta-lactams have  
 2396 stability issues (e.g. amoxicillin and clavulanic acid), precluding 24 hour infusion preparations. For these  
 2397 beta-lactam agents extended intermittent infusion would be appropriate. Of note, while most  $\beta$ -  
 2398 lactams have a half-life of 1–2 hours and therefore often benefit from prolonged or continuous infusion

2399 to optimize pharmacokinetic targets, agents with longer half-lives—such as ceftriaxone ( $\approx$ 8 hours)—  
2400 might theoretically achieve comparable pharmacodynamic exposure with intermittent twice-daily  
2401 dosing. In critically ill patients, however, the earlier described sepsis-related alterations in clearance  
2402 and volume of distribution make drug concentrations far less predictable. These mechanisms suggest  
2403 that even  $\beta$ -lactams with a long half-life may perform better when administered as prolonged infusion  
2404 rather than intermittent dosing in the ICU setting. A key challenge for future studies will be to identify  
2405 which subgroups benefit most from such optimization strategies, for example patients with  
2406 augmented renal clearance.<sup>293</sup>

2407

2408 Formulating recommendations on aminoglycoside dosing is complicated due to the wide range of  
2409 aminoglycoside concentrations found in patients with sepsis after low or high doses of  
2410 aminoglycosides.<sup>294-296</sup> This wide range results in a percentage of patients with subtherapeutic  
2411 concentrations (based on PK/PD models) and a percentage of patients with overexposure to the drug.  
2412 Overexposure to amikacin was associated with increased mortality in the observational study of Allou  
2413 et al in severe sepsis and septic shock patients.<sup>294</sup> On the other hand, the authors showed that patients  
2414 reaching the PK/PD target had reduced mortality compared to those not reaching the target.<sup>283</sup> PK/PD  
2415 models confirm difficulties of target attainment in aminoglycoside treatment, especially in infections  
2416 with bacteria with higher MICs.<sup>249</sup> Recently, EUCAST changed aminoglycoside breakpoints based on  
2417 PK/PD-based modelling after a general consultation round.<sup>297</sup> EUCAST concluded that for serious  
2418 infections targets for efficacy cannot be reached and consequently do not provide breakpoints for  
2419 patients with systemic infections anymore. In those infections, EUCAST suggests that aminoglycosides  
2420 should be used in combination with other active therapy and provide aminoglycoside MIC's to  
2421 distinguish between bacteria with and without acquired resistance mechanisms.<sup>44</sup> Based on the same  
2422 principles, EUCAST now advises against gentamicin for *P. aeruginosa* infections. Uncertainty of target  
2423 attainment and risk of toxicity are therefore a major disadvantage of aminoglycoside treatment of  
2424 patients with sepsis.

2425

2426 Two observational studies reported that active pharmacokinetic dosing (including information on  
2427 trough levels) was associated with increased clinical efficacy and decreased toxicity compared to  
2428 standard dosing.<sup>298, 299</sup> Taking in mind the wide variation of aminoglycoside concentrations in patients  
2429 with sepsis, the committee recommends to implement individualized pharmacokinetic dosing,  
2430 including direct therapeutic drug monitoring of aminoglycosides in patients with sepsis, in order to  
2431 reduce subtherapeutic concentrations and overexposure to aminoglycosides. We suggest that either  
2432 mid-dosing or both peak and trough concentrations are measured and that dosing is adjusted  
2433 according to the guidance of the clinical pharmacist. In the Netherlands, gentamicin and tobramycin  
2434 doses of 5 mg/kg are recommended in adults with infections in general by the NVZA.<sup>300</sup> Doses of 6  
2435 mg/kg (tobramycin) or 6-7 mg/kg (gentamicin) are suggested for ICU patients or patients with sepsis.<sup>300</sup>  
2436 EUCAST now suggests gentamicin and tobramycin doses of 6-7 mg/kg.<sup>44</sup> The SWAB guideline  
2437 committee did not reach consensus on the question if one should use higher initial aminoglycoside  
2438 dosing in patients with sepsis and septic shock because of lack of clinical data on toxicity in patients  
2439 treated with higher initial doses. Although the committee is concerned about the efficacy and toxicity  
2440 of aminoglycosides based on available clinical evidence and the suggestions based on PK/PD models  
2441 by EUCAST, we felt that at this point there is insufficient evidence to recommend against  
2442 aminoglycosides in patients with sepsis in general or against the specific use of empirical gentamicin  
2443 in patients with a higher likelihood of involvement of *P. aeruginosa*. In the coming years a large Dutch

2444 randomized controlled trial will assess the efficacy and safety of empirical aminoglycoside therapy in  
2445 patients with sepsis.

2446

2447 Regarding vancomycin, there is lack of high quality studies on optimal dosing of vancomycin.<sup>301</sup> Very  
2448 low quality evidence suggests that continuous infusion could decrease the risk of nephrotoxicity in  
2449 patients with severe MRSA infections. There is no evidence on effect on other clinical outcomes. Also,  
2450 the clinical consequences of nephrotoxicity haven't been studied. Use of TDM in general in vancomycin  
2451 is associated with improved clinical efficacy and reduced renal toxicity as was shown in mainly  
2452 observational studies in non-sepsis patient population.<sup>302</sup> One systematic review concluded that  
2453 continuous infusion of vancomycin may be cheaper and TDM easier to perform than intermittent  
2454 infusion.<sup>303</sup> In the Netherlands, most patients treated with vancomycin are treated for infection with  
2455 coagulase negative staphylococci (CNS) or *E. faecium* which are less virulent than MRSA. Some patients  
2456 with *S. aureus* infections and contra-indications for beta-lactams may be treated with vancomycin.  
2457 Current practice in the Netherlands varies, with some hospitals providing continuous infusion, while  
2458 many provide intermittent dosing.<sup>303</sup> A practical advantage of continuous infusion is that drug  
2459 concentration can be measured any time after reaching steady state. Practical disadvantages for  
2460 continuous infusion could be the need for extra venous access and the incompatibility with other  
2461 medication. The SWAB guideline committee therefore agreed to suggest continuous infusion of  
2462 vancomycin in patients with sepsis. Since vancomycin TDM is widely available, we recommend  
2463 performing early TDM in patients with sepsis, i.e. 24 hour after the start.

2464

2465 For ciprofloxacin, several PK/PD studies have been published using clinical data of patients with  
2466 moderate to severe infections, septic shock and/or of critically ill patients. Although the studies used  
2467 different PK/PD targets, they show no concerns about ciprofloxacin target attainment of regular dosing  
2468 (two times 400 mg iv per 24h) when bacteria with MICs <0.125 mg/L are involved.<sup>304-307</sup> In contrast,  
2469 these and other studies showed it is difficult or impossible to reach the PK/PD target when bacteria  
2470 with MICs ≥0.5 mg/L are involved.<sup>304-309</sup> Higher dosing (three times 400 mg iv per 24h) was only  
2471 moderately effective to increase target attainment when bacteria with MICs between 0.125 and 0.5  
2472 mg/L were involved. In a study of Enterobacterales bacteraemia three times daily ciprofloxacin dosing  
2473 increased percentage target attainment (defined as fAUC/MIC>250) for bacteria with MICs of 0.125  
2474 and 0.25 mg/L from approximately 70 to 95% and 10 to 40% respectively.<sup>307</sup> Three times daily dosing  
2475 in a Dutch study of critically ill patients increased percentage target attainment (defined as  
2476 fAUC/MIC>125) for bacteria with MICs of 0.25 and 0.5 mg/L from approximately 95 to 100 and 40 to  
2477 70% respectively.<sup>306</sup> Ciprofloxacin is generally well tolerated.<sup>310</sup> Ciprofloxacin in higher doses (three  
2478 times daily 400 mg iv) is also reported to be safe in small studies.<sup>310, 311</sup> EUCAST epidemiological cut-  
2479 offs (ECOFF) for most Enterobacterales are 0.125 mg/L and clinical breakpoints 0.25 mg/L.<sup>44</sup> Higher  
2480 ECOFFs are reported for *Pseudomonas* species (0.5 mg/L), *Acinetobacter* species (1 mg/L) and  
2481 *Staphylococcus* species (1 mg/L). Clinical breakpoints of these three species are therefore based on  
2482 high dose ciprofloxacin therapy (three times daily 400 mg iv) by EUCAST. In general, ciprofloxacin  
2483 monotherapy is not recommend as monotherapy for *S. aureus* infections.

2484

2485 Overall, the available evidence indicates that ciprofloxacin efficacy is mainly dependent of MIC of the  
2486 involved bacteria. The committee would like to emphasize that the available evidence shows  
2487 suboptimal target attainment of ciprofloxacin treatment when bacteria with MIC 0.5 mg/L or higher  
2488 are involved, even with higher dosing of ciprofloxacin. In patients with sepsis and risk of involvement

2489 of bacteria with MIC 0.5 mg/L or higher, we therefore suggest against ciprofloxacin monotherapy as  
 2490 the first therapy of choice. If local epidemiology is such that most Enterobacterales show MICs of 0.125  
 2491 to 0.25 mg/L, the available evidence supports three times daily dosing. In line with EUCAST  
 2492 recommendations, we support a three times daily dosing schedule for *Pseudomonas*, *Acinetobacter*  
 2493 spp. and *S. aureus* infections, but prefer other antibiotic classes for initial therapy of patients with  
 2494 sepsis due to these bacteria.<sup>44</sup>

2495  
 2496 Some observational studies in critically ill obese patients evaluating PK parameters are available.<sup>312-318</sup>  
 2497 One case-control study evaluated the differences in ceftazidime, piperacillin-tazobactam and  
 2498 meropenem concentration between obese and non-obese patients. No major differences were  
 2499 observed. The study showed that sepsis had a greater impact on differences in PK-parameters than  
 2500 obesity itself.<sup>315</sup> This finding is consistent with an observational study in obese ICU patients defining  
 2501 steady state meropenem concentrations.<sup>314</sup> It showed that although steady state volume of  
 2502 distribution was increased, the standard dosing regimen achieved an adequate probability of target  
 2503 attainment. Another prospective, observational study found that obese ICU patients were at risk of  
 2504 overdosing.<sup>316</sup> However, the evidence for the validity of a piperacillin toxicity cut-off value is poor. Two  
 2505 studies showed that underdosing of meropenem and piperacillin in obese critically ill patients may  
 2506 result from augmented renal function during sepsis in obese patients, especially during intermittent  
 2507 dosing.<sup>312, 313</sup>

2508  
 2509 One systematic review summarized a limited number of studies on pharmacokinetic parameters of  
 2510 aminoglycosides in critically ill, obese patients.<sup>318</sup> Very limited data showed that dose adjustment and  
 2511 TDM of aminoglycosides based on PK/PD principles may improve target attainment in critically ill,  
 2512 obese patients. One retrospective study showed that obese ICU patients treated with continuous  
 2513 vancomycin required lower maintenance dosing than non-obese patients.<sup>317</sup>

2514  
 2515 The committee concluded that overall the limited evidence on beta-lactam pharmacokinetics in obese  
 2516 patients with sepsis suggests that sepsis characteristics influence PK/PD parameters more than  
 2517 obesity. Current data do not support a different approach of beta-lactam dosing in obese patients with  
 2518 sepsis compared to non-obese patients. For aminoglycosides and vancomycin, the committee  
 2519 concluded that the limited evidence supports dose adjustment in obese patients with sepsis. Similar  
 2520 to non-obese patients, evidence supports TDM of aminoglycosides and vancomycin in obese patients  
 2521 with sepsis.

2522  
 2523 **Recommendations**

Recommendation	Strength	Quality of evidence
46. In patients with sepsis, we suggest that dosing strategies of antibacterial therapy be optimized based on accepted pharmacokinetic / pharmacodynamic principles and specific drug properties ( <b>Table 10</b> )	Weak	Low
47. For adults with sepsis or septic shock treated on the intensive care unit, we recommend prolonged infusion of piperacillin-tazobactam or	Strong	High

carbapenems for maintenance (after an initial loading dose) rather than bolus administration.		
48. For adults with sepsis or septic shock treated on the intensive care unit, we suggest prolonged infusion rather than bolus administration for other beta-lactams such as cephalosporines/penicillins, taking their pharmacokinetic properties into account.	Weak	Low to moderate
49. In patients with sepsis, we recommend direct therapeutic drug monitoring (including either mid-dosing or both peak and through levels) during aminoglycoside treatment in patients with sepsis and septic shock	Strong	GPS
50. In patients with sepsis, we recommend therapeutic drug monitoring during vancomycin treatment in patients with sepsis and septic shock	Strong	GPS
51. In patients with sepsis, we suggest therapeutic drug monitoring when there are concerns on target attainment of other antibacterial drugs than aminoglycoside and vancomycin (e.g. extreme body weight, augmented or decreased renal clearance, hypoalbuminemia)	Weak	GPS
52. In patients with sepsis, we suggest continuous* infusion of vancomycin	Weak	GPS
53. In patients with sepsis in whom ciprofloxacin is indicated, we suggest empirical ciprofloxacin three times daily 400 mg iv	Weak	GPS

\* Continuous infusion includes one intermittent dose as a loading dose

2524  
2525  
2526

**Table 10. Recommended iv doses of empirical antibacterial treatment for sepsis**

Antibacterial agent	Intermittent dosing (<60 min infusion)	Prolonged dosing (3-5 hour infusion)	Continuous infusion + loading dose	Remarks
Benzylpenicillin	6x 1 million IU	6x 1 million IU	6 million IU + 1 million IU loading dose	Higher doses optional up to 24 million IU per 24h*
Amoxicillin	6x 1000 mg	6x 1000 mg	6000 mg + 1000 mg loading dose	Higher doses optional up to 12000 mg per 24h*
Flucloxacillin	6x 1000 mg	6x 1000 mg	6000 mg + 1000 mg loading dose	Higher doses optional up to 12000 mg per 24h*
Amoxicillin-clavulanic acid	4x 1200 mg	4x 1200 mg	N.a.	
Piperacillin-tazobactam	4x 4500 mg	4x 4500 mg	18000 mg + 4500 mg loading dose	3x 4500 mg when <i>Pseudomonas</i> is not involved*
Cefazolin	3x 1000 mg	3x 1000 mg	3000 mg + 1000 mg loading dose	Higher doses optional up to 6000 mg per 24h*
Cefuroxime	3x 1500 mg	3x 1500 mg	4500 mg + 1500 mg loading dose	
Ceftriaxone	1x2000 mg	1x 2000 mg	2000 mg + 2000 mg loading dose	2x 2000 mg when <i>S. aureus</i> is involved*
Ceftazidime	3x 2000 mg	3x 2000 mg (3 hour infusion)	6000 mg + 2000 mg loading dose	3x 1000 mg or 3000 mg per 24h + 1000 mg loading dose optional when <i>Pseudomonas</i> is not involved
Imipenem	4x 1000 mg	4x 1000 mg	4000 mg + 1000 mg loading dose	4x 500 mg optional when <i>Pseudomonas</i> is not involved
Meropenem	3x 1000 mg	3x 1000 mg (3 hour infusion)	3000 mg + 1000 mg loading dose	Higher doses optional up to 6000 mg per 24h*
Ciprofloxacin	3x 400 mg	N.a.	N.a.	2x 400 mg when <i>Pseudomonas</i> is not involved*
Gentamicin	1x 5 mg/kg**	N.a.	N.a.	1x 6-7 mg/kg may be indicated in sepsis due to Enterobacterales * Adjusted for adjusted body weight** Immediate TDM recommended*** Should be given in combination with other antibacterial therapy, generally a beta-lactam agent. Gentamicin may be a suboptimal choice for <i>P. aeruginosa</i> based on PK/PD models****
Tobramycin	1x 5 mg/kg**	N.a.	N.a.	1x 6-7 mg/kg may be indicated in sepsis due to Enterobacterales or <i>Pseudomonas</i> * Adjusted for adjusted body weight** Immediate TDM recommended***

				Should be given in combination with other antibacterial therapy, generally a beta-lactam agent.****
Vancomycin	2-3x 15-20 mg/kg + 25-30 mg/kg loading dose	N.a.	30-40 mg/kg + 15-20 mg/kg loading dose	Adjusted for adjusted body weight** TDM recommended***
Metronidazole	3x 500 mg	N.a.	N.a.	
Trimethoprim-sulfamethoxazole	2x 960 mg	N.a.	N.a.	Higher doses optional*

2528 \* See also EUCAST dosing table (<http://www.eucast.org/>) for guidance on which pathogens may require higher dosing and other relevant guidelines for  
2529 infections that require other dosages. In case of higher 24h doses a higher loading dose is indicated (i.e. one intermittent dose)

2530 \*\* Adjusted for adjusted body weight (ideal body weight + 0,4\*(true body weight – ideal body weight. Ideal body weight: man: 50 kg + 0,9 \* (cm > 150 cm);  
2531 woman: 45 kg + 0,9 \* (cm > 150 cm). See <https://tdm-monografie.org/>

2532 \*\*\* See <https://tdm-monografie.org/>

2533 \*\*\*\* Since 2020 EUCAST doesn't provide formal breakpoints for aminoglycosides in systemic infection (excluding UTI) with Enterobacterales, *Pseudomonas*,  
2534 *Acinetobacter* and *Staphylococcus* species anymore. EUCAST recommends that in systemic infections with these species, the aminoglycoside must be  
2535 supported by other active therapy. In addition, there are no breakpoints for gentamicin in any infection with *Pseudomonas* species anymore. See EUCAST  
2536 clinical breakpoints table and [http://www.eucast.org/guidance\\_documents/](http://www.eucast.org/guidance_documents/).

2537

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2542 2024 NethMap data.

## 2543 Appendix

2544

### 2545 Literature searches

#### 2546 1. Which bacteria are most frequently isolated from patients with sepsis in the 2547 Netherlands?

2548 For chapter 1 we searched for epidemiological studies on bacterial aetiology of sepsis and resistance  
2549 patterns. We focussed on studies from the Netherlands. We also used NethMap 2017 data and the  
2550 PREZIES database.<sup>43</sup> NethMap is an annual report, published by the SWAB in collaboration with the  
2551 National Institute for Public Health and the Environment of the Netherlands (RIVM). It contains data  
2552 from ongoing surveillance of antibacterial agents and resistance among common human pathogens.

2553

2554 In addition, we requested information on pathogens causing central venous catheter infections from  
2555 the Dutch national AMR surveillance system (Infectious Diseases Surveillance Information System for  
2556 Antimicrobial Resistance or ISIS-AR).<sup>61</sup> For this search, all 2017 cultures categorized as catheter tip or  
2557 blood were selected. Blood cultures (BC) taken from lines (documented as BC taken from a line) were  
2558 excluded. Central venous catheter infection was identified when a peripheral blood culture and a tip  
2559 culture were both positive within a maximum of one day difference (before or after) in the date of  
2560 taking the sample into process, growing the same microorganism. If a patient had more than one “set”  
2561 meeting this definition, only the first positive set was evaluated.

2562

2563 For the update of the guideline, we updated NethMap surveillance data with data from 2024.<sup>28</sup> In  
2564 addition, we added relevant results from Dutch sepsis trials that were conducted or reported since the  
2565 previous guideline version.

#### 2566 2. What are the resistance patterns of the most frequently isolated bacteria in 2567 patients with sepsis in the Netherlands?

2568 For chapter 2 we used studies from the Netherlands found for chapter 1a and NethMap data from  
2569 2017 and 2024.<sup>28</sup> In addition, we requested additional resistance data from the Dutch national AMR  
2570 surveillance system (Infectious Diseases Surveillance Information System for Antimicrobial Resistance  
2571 or ISIS-AR).<sup>61</sup>

2572 **3. Which patients are at risk for sepsis due to third-generation cephalosporin-**  
2573 **resistant Enterobacterales (3GCR-E) or *P. aeruginosa* in the Netherlands?**

2574 For chapter 3, we restricted the evidence summary to systematic reviews, externally validated  
2575 prediction rules and Dutch cohort studies on risk factors for sepsis or severe infections with  
2576 Enterobacterales resistant to third-generation cephalosporins (3GCR-E) or with *P. aeruginosa*. We also  
2577 included studies on HRMO (gram-negatives) in general and a large systematic review that assessed risk  
2578 factors for inappropriate empirical therapy.

2579  
2580 We focussed our search on evidence on risk factors for sepsis due the HRMO that are most frequently  
2581 encountered in the Netherlands: Enterobacterales resistant to 3<sup>rd</sup> generation cephalosporins or shown  
2582 to harbour ESBL or AmpC genes. Sepsis due to these microorganisms would not be appropriately  
2583 treated with current general empirical therapy recommendations.<sup>29</sup> We did not systematically search  
2584 for risk factors for sepsis due to other HRMOs, i.e. Enterobacterales resistant to both fluoroquinolones  
2585 and aminoglycosides, *P. aeruginosa* resistant to  $\geq 3$  antibacterial therapy groups (among  
2586 fluoroquinolones, aminoglycosides, carbapenems, ceftazidime and piperacillin-tazobactam) and  
2587 *Acinetobacter spp.* resistant to imipenem or meropenem or resistant to both fluoroquinolones and  
2588 aminoglycosides. Due to the low prevalence of sepsis due carbapenemase-producing gram-negative  
2589 bacteria, penicillin-resistant *S. pneumoniae* and *N. meningitidis*, MRSA or VRE in the Netherlands we  
2590 did not include studies on risk factors for sepsis due to these bacteria.<sup>43, 319</sup>

2591 **4. What is the importance of appropriate empirical therapy in patients with**  
2592 **sepsis?**

2593 For this key question we used the literature and grading presented in the SSC 2016 guideline, IDSA  
2594 guideline on HAP/VAP and SIS guideline on intra-abdominal infections.<sup>37-39</sup> In addition, we referred to  
2595 the SWAB guideline on management of complicated urinary tract infections and the Dutch evidence-  
2596 based guideline on necrotizing soft tissue infections (2015).<sup>4, 6</sup> An additional search for relevant  
2597 studies on the topic led to five systematic reviews and two RCTs.<sup>86, 90-95</sup>

2598 **5. What is the effect of double active empirical antibiotic therapy compared to**  
2599 **monotherapy in patients with sepsis?**

2600 For this key question we used the literature and grading presented in the SSC 2016 guideline, IDSA  
2601 guideline on HAP/VAP.<sup>37, 38</sup> In addition, we referred to the Dutch guideline on *S. aureus* bacteraemia.<sup>8</sup>  
2602 An additional search for relevant studies on the topic led to three systematic reviews and one RCT.<sup>108,</sup>  
2603 <sup>112-114</sup>

2604 **6. What is the optimal choice of empirical therapy in patients with sepsis in The**  
2605 **Netherlands**

2606 For this key question we used the literature and grading presented in the SSC 2016 guideline, IDSA  
2607 guideline on HAP/VAP and SIS guideline on intra-abdominal infections.<sup>37-39</sup> An additional search for  
2608 studies published since the searches of these guidelines led to 12 systematic reviews and two RCTs.<sup>92,</sup>

2609 114, 136-140, 142, 155-160 Due to the low prevalence of sepsis due to MRSA in the Netherlands we did not  
 2610 include studies on empirical treatment of sepsis and risk of involvement of MRSA. We did not  
 2611 summarize evidence on treatment of necrotizing pancreatitis and sepsis due to diabetic foot infection.  
 2612

2613 We additionally performed a search of all relevant studies published from June 2008 until October  
 2614 2018 in MEDLINE and PubMed databases, for the following question:

- What is the optimal empirical therapy for a suspected central catheter infection?

2615  
 2616  
 2617 All abstracts were screened for relevance. The specific search strategies are described in **Table A**. These  
 2618 results were added to the literature presented in the IDSA Guideline 2009 for catheter related  
 2619 infections.  
 2620

2621 **Table A. Search strategy empirical therapy in sepsis due to suspected infected CVC**

Search no.	Query	results	relevant
1	"Catheter-Related Infections/diagnosis"[Mesh] AND "Terminology as Topic"[Mesh] AND (Dutch[lang] OR English[lang])	3	1
2	"catheter related bloodstream infection defining [TIAB]"	10	1
3	((("Catheter-Related Infections/epidemiology"[Mesh]) OR "Catheter-Related Infections/microbiology"[Mesh]) AND "Cross Infection/microbiology"[Mesh]) AND "Bacteremia/microbiology"[Mesh]	111	10
4	((("Catheter-Related Infections"[Mesh]) AND "Anti-Bacterial Agents/therapeutic use"[Mesh]) AND "Clinical Trials as Topic"[Mesh])	18	0
5	((("Catheter-Related Infections"[Mesh]) AND "Anti-Bacterial Agents/therapeutic use"[Mesh]) AND "Randomized Controlled Trial"[pt])	29	1
6	((("Catheter-Related Infections"[Mesh]) AND "Anti-Bacterial Agents/therapeutic use"[Mesh]) AND "empiric"[TIAB])	25	1
7	((("Catheter-Related Infections"[Mesh]) AND "Anti-Bacterial Agents/therapeutic use"[Mesh])) AND "Teicoplanin"[Mesh]	7	0
8	((("Catheter-Related Infections"[Mesh]) AND "Anti-Bacterial Agents/therapeutic use"[Mesh])) AND ("Prostheses and Implants"[Mesh])	8	0
9	((("Catheter-Related Infections"[Mesh]) AND "Anti-Bacterial Agents/therapeutic use"[Mesh])) AND "Prosthesis-Related Infections"[Mesh]	8	0
10	((("Catheter-Related Infections"[Mesh])) AND "Prosthesis-Related Infections"[Mesh])	47	1
11	"Catheter-Related Infections"[Mesh] AND "Candidemia"[Mesh]	89	1
12	"Anti-Bacterial Agents/therapeutic use"[Mesh] AND "tunneled catheter"	16	0
13	"Anti-Bacterial Agents/therapeutic use"[Mesh] AND "Hickman"[TIAB]	65	0
14	"Coagulase-Negative Staphylococci [tiab] and/or enterococci [tiab] and joint infections [tiab]"	120	1

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For chapter 6b we focussed on evidence for treatment efficacy for sepsis due the HRMO that are most frequently encountered in the Netherlands: Enterobacterales resistant to 3<sup>rd</sup> generation cephalosporins or have shown to harbour ESBL or AmpC genes (3GCR-E). Sepsis due to these microorganisms would not be appropriately treated with current general empirical therapy recommendations.<sup>29</sup> We did not systematically search for risk factors for sepsis due to other HRMOs. In addition, we did not systematically summarize antibacterial agents that are currently not easily available in the Netherlands, such as ampicillin/sulbactam, ceftiofex, cefepime, ceftazidime/sulbactam and doripenem.

For chapter 6c we performed a literature search on the efficacy and safety of empirical treatment with 3<sup>rd</sup> generation cephalosporins in patients with sepsis due to *S. aureus* infections. For definite treatment of sepsis due to *S. aureus* we refer to the NVMM guideline on *S. aureus* bacteraemia.

## **7. What is the optimal timing of empirical antibacterial therapy in patients with sepsis?**

For this key question, we used the literature as presented in the SSC 2016 guidelines, chapter on antibacterial therapy.<sup>37</sup> An additional search for studies published since the SSC guidelines led to one RCT. In addition, we included two large landmark observational studies to our evidence summary.

## **8. What is the optimal duration of antibacterial treatment for sepsis?**

For this key question, we used the literature presented in the SSC 2016 guideline, IDSA guideline on HAP/VAP 2016 and SWAB guideline on antimicrobial stewardship 2016.<sup>37, 38, 41</sup> An additional search for studies published since the SSC search for this question led to new meta-analyses on PCT-guided antibiotic treatment duration.<sup>220-222</sup> Also, a consensus statement on antimicrobial de-escalation in critically ill patients from the European Society of Intensive Care Medicine (ESICM) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) was used for relevant literature on de-escalation in patients with sepsis.<sup>241</sup>

For the 2025 SWAB sepsis guideline update, we additionally performed a comprehensive search for literature on the optimal antibacterial treatment duration in patients with gram-negative bacteraemia. We searched for studies published since the literature search of the previous SWAB sepsis Guideline, with the help of a Medical Information Retrieval Specialist. We searched Medline (Ovid) and Embase (Ovid) for randomized controlled trials (RCTs) and systematic reviews and meta-analysis published between January 2020 and August 2025.

- P: Hospitalized adult patients with gram-negative bacteraemia**
- I: Treatment duration ≤7 days**
- C: Treatment duration >7 days**
- O: Mortality, readmission after discharge, relapse of bacteraemia**
- S: Systematic reviews, randomized controlled trials**

2663 T: January 2020 - August 2025

2664

2665 We identified 861 RCTs and 510 systematic review and meta-analyses. After screening titles and  
2666 abstracts, eight studies were considered potentially relevant: four high quality RCTs [11-14] and four  
2667 high quality systematic review and meta-analyses [15-18]. Three systematic review and meta-analyses  
2668 covered four RCTs, including three RCTs identified in our search and the study performed by Yahav et  
2669 al [10], discussed in the previous guideline. One systematic review and meta-analysis included three  
2670 RCTs. [10,12,13] Since several systematic reviews used the GRADE system to rate the certainty of  
2671 evidence, we adopted the GRADE assessments as reported in these reviews.

2672 **9. In patients with sepsis, should we recommend pharmacokinetic /**  
2673 **pharmacodynamic dosing optimization for empirical antibacterial therapy?**

2674 For this key question we used the literature and grading presented in the SSC 2016 guideline and IDSA  
2675 guideline on HAP/VAP.<sup>37, 38</sup> An additional search for studies published since the SSC search for this  
2676 question led to a clinical practice guideline and systematic review on vancomycin.<sup>288, 301</sup>

2677

2678 For the 2025 SWAB sepsis guideline update, we additionally performed a comprehensive search for  
2679 literature comparing intermittent infusion versus prolonged infusion of beta-lactam antibiotics in  
2680 patients with sepsis. The search was done for the last 5 years (2020-June 2025), as our previous  
2681 guideline included studies until 2020. We used the Medline database.

2682

2683 P: Adults with sepsis

2684 I: Prolonged infusion of intravenous beta-lactam antibiotics (antibiotic infused over at least half of the  
2685 dosing interval or continues infusion)

2686 C: Intermittent infusion of beta-lactam antibiotics (infusion ≤ 30 minutes)

2687 O: Mortality <30 and <90 days after start of therapy, clinical improvement within 72 hours, ICU  
2688 admission, length of hospital stay, duration of antibiotic treatment, duration of IV antibiotic treatment,  
2689 duration of broad-spectrum antibiotic treatment

2690 S: Systematic reviews, RCTs

2691 T: 2020-2025

2692

2693 Using this search, we identified 39 studies. After screening titles and abstracts, eight studies were  
2694 considered potentially relevant: five were systematic reviews and/or meta-analyses, and three were  
2695 randomized controlled trials (RCTs).

2696

2697 Following full-text review, we identified one systematic review [5] that included all relevant studies  
2698 cited in the remaining four systematic reviews. The other four reviews also included a few additional  
2699 RCTs; however, these involved patient populations outside our inclusion criteria (i.e., non-septic  
2700 patients or neonates/children) or focused on pharmacokinetic/pharmacodynamic outcomes.

2701 Of the three RCTs, two were already included in the systematic review by Abdul-Aziz et al. For this  
2702 guideline, we therefore chose to include the systematic review by Abdul-Aziz et al. [5], supplemented  
2703 by the RCT conducted by Khan et al. [6].

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CONCEPT

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